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Review

Selenoproteins and selenium status in bone physiology and pathology

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ABSTRACT

Background: Emerging evidence supports the view that selenoproteins are essential for maintaining bone health.
Scope of review: The current state of knowledge concerning selenoproteins and Se status in bone physiology and pathology is summarized.
Major conclusions: Antioxidant selenoproteins including glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), as a whole, play a pivotal role in maintaining bone homeostasis and protecting against bone loss. GPx1, a major antioxidant enzyme in osteoclasts, is up-regulated by estrogen, an endogenous inhibitor of osteoclastogenesis. TrxR1 is an immediate early gene in response to 1α,25-dihydroxyvitamin D3, an osteoblastic differentiation agent. The combination of 1α,25-dihydroxyvitamin D3 and Se generates a synergistic elevation of TrxR activity in Se-deficient osteoblasts. Of particular concern, pleiotropic TrxR1 is implicated in promoting NFκB activation. Coincidentally, TrxR inhibitors such as curcumin and gold compounds exhibit potent osteoclastogenesis inhibitory activity. Studies in patients with the mutations of selenocysteine insertion sequence-binding protein 2, a key trans-acting factor for the co-translational insertion of selenocysteine into selenoproteins have clearly established a causal link of selenoproteins in bone development. Se transport to bone relies on selenoprotein P. Plasma selenoprotein P concentrations have been found to be positively correlated with bone mineral density in elderly women.
General significance: A full understanding of the role and function of selenoproteins and Se status on bone physiology and pathology may lead to effectively prevent against or modify bone diseases by using Se.

1. Introduction

The physiological functions of the essential micronutrient selenium (Se) are mediated principally through a class of selenocysteine (Sec)-containing proteins referred to as selenoproteins. The 25 selenoproteins found in humans are glutathione peroxidases (GPx1, 2, 3, 4, 6), thioredoxin reductases (TrxR1, 2, 3), iodothyronine deiodinases (Dio1, 2, 3), selenophosphate synthetase 2, 15 kDa selenoprotein, and selenoprotein H, I, K, M, N, O, P, R, S, T, V, and W [1–4], of which many act as a redox gatekeeper and play an important role in maintaining cellular antioxidant homeostasis [1–4].

The core part of the selenoprotein biosynthesis machinery is the co-translational incorporation of Sec, the 21st amino acid, into the growing polypeptide. Two distinct features are included in this multi-stage process (Fig. 1A): 1) UGA generally acts as the termination codon in protein translation; unusually, Sec insertion is dictated by an in-frame UGA provided that it is followed by a Sec insertion sequence (SECIS) element; 2) upon the binding of SECIS-binding protein 2 (SBP2) to the SECIS element, Sec-tRNA$^{[Ser]Sec}$ is recruited to provide Sec; uniquely, Sec synthesis from Se metabolites is confined on Sec-tRNA$^{[Ser]Sec}$ because Sec is a highly reactive amino acid with an exceptionally low pKa value of 5.2, so that there is no free pool of Sec [3,5,6]. Although these demanding steps are inefficient and energy-intensive, the evolutionary pressure for the preservation of selenoproteins and their conservation among species are attributed to the fact that Sec within enzymes has extraordinarily high nucleophilicity and confers resistance to oxidant-induced inactivation compared with cysteine (Cys), thus allowing selenoenzymes to turn over diverse substrates much better and to have 10- to 100-fold higher activities than Sec-to-Cys nonselenoprotein mutants [7–12].

Among the various selenoproteins found in humans, the biological functions of the GPx and TrxR families have been well elucidated. GPx reduces hydrogen peroxide or other hydroperoxides to water or alcohols using glutathione (GSH) as a reductant. GPx knockout mice are sensitive to hydroperoxide challenges, which suggests that this class of selenoenzymes functions as antioxidants [13–16]. Thioredoxin (Trx) participates in a broad range of cellular functions, including the reduction of peroxides, activation of redox-sensitive transcription factors via reduction of their conserved Cys residues that are required for DNA-binding, and apoptosis inhibition through binding apoptosis signal-regulating kinase 1 [17]. The functions of Trx rely on its reduced form, whereas TrxR is a specific enzyme responsible for catalyzing the

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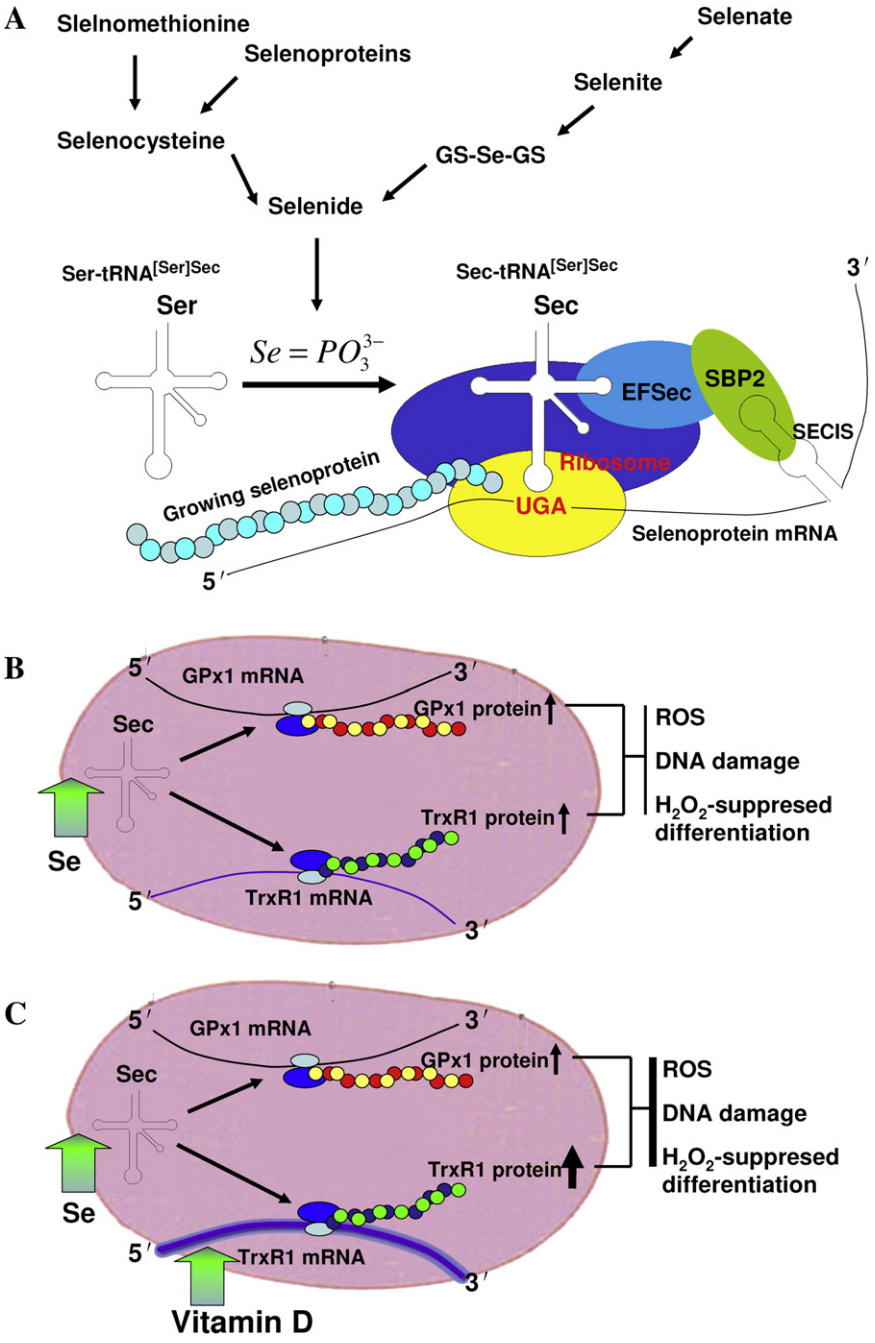

Fig. 1. Biosynthesis of selenoproteins and synergistic effect of 1α,25(OH)2D3 and Se on TrxR1 activity in osteoblasts. (A) Co-translational incorporation of Sec into selenoprotein occurs at the UGA codon. SBP2 recognizes the SECIS element equipped in all mRNAs encoding selenoprotein. Upon the combination of EFSec (elongation factor of Sec) with SBP2, Sec-loaded tRNA $^{[Ser]Sec}$ is recruited to ribosome. (B) Se supplementation increases GPx and TrxR activities, consequently reducing intracellular ROS levels and DNA damage and counteracting hydrogen peroxide-suppressed osteoblastic differentiation. (C) Co-treatment of 1α,25(OH)2D3 and Se synergistically elevates TrxR1 protein and activity in Se-deficient hFOB through concerted regulation of transcription and translation.

reduction of the active site disulfide of Trx using nicotinamide-adenine dinucleotide phosphate (NADPH). Therefore, TrxR is implicated in regulating numerous biological functions [18–22].

Inadequate Se intake that compromises selenoprotein biosynthesis has long been known to be detrimental to health, including bone well-being [23–26]. On the other hand, a growing body of evidence shows that Se at supranutritional levels, which exceed the requirement for selenoprotein biosynthesis, is able to modify some pathological alterations via various mechanisms, such as suppressing NFκB activation and inflammatory reactions [27–34], activating p53 and DNA repair [35–38], inducing chemoprotective enzymes [39–41], and inhibiting proliferation or promoting apoptosis [42–44]. The potential pharmacological effects of Se at supranutritional levels are principally mediated by low-molecular weight Se metabolites including selenodiglutathione and methylselenol, which have a highly reactive nature since the Se moiety in these selenocompounds has strong nucleophilicity [45–48].

Healthy skeletal remodeling is maintained by an elegant equilibrium between the activities of mesenchymal stem cell-derived osteoblasts and hematopoesis-derived osteoclasts on the bone surface. Osteoblasts that deposit extracellular organic matrix in an orderly fashion are responsible for new bone formation, whereas multinucleated giant osteoclasts facilitate old bone degradation through secreting acid and lytic

enzymes [49]. The molecular triad of receptor activator of NFκB ligand (RANKL) expressed by osteoblast lineage cells, osteoprotegerin (OPG) produced by osteoblastic/stromal cells, and receptor activator of NFκB (RANK) on osteoclasts functions as a pivotal signal link for osteoblast and osteoclast coupling [50–53]. RANKL stimulates osteoclastic differentiation by binding RANK. OPG, acting as a decoy receptor for RANKL, blocks RANKL/RANK interactions and inhibits the terminal stages of osteoclastic differentiation. Once the coupling is significantly disturbed without timely repair, various types of bone diseases, such as osteopetrosis, osteoarthritis, osteoporosis, or osteolysis, tend to occur [53]. Oxidative stress with an increased level of reactive oxygen species (ROS) being present in the bone system is deleterious to normal bone physiology because excessive amounts of ROS suppress osteoblastic differentiation and promote osteoclastic differentiation along with NFκB activation independently [54,55]. Moreover, excessive amounts of ROS orchestrate a crosstalk between cells of the osteoblastic and osteoclastic lineages in favor of osteoclastogenesis; namely, ROS stimulates RANKL expression in osteoblasts [56] and acts as a crucial intracellular signal mediator for RANKL-stimulated osteoclastic differentiation [57,58]. Approaches that scavenge ROS in excess of physiological requirements or suppress NFκB activation have been validated to be highly efficient in inhibiting osteoclastogenesis [57,58]. The goal of this article is to contextualize the information regarding selenoproteins in osteoblasts and osteoclasts as well as Se status in bone homeostasis and disorders, to provide an overview of the current state of knowledge of Se in bone physiology and pathology.

2. Selenoproteins in osteoblasts and osteoclasts

Most of the known selenoprotein genes and some important factors required for selenoprotein biosynthesis have been found in either osteoblasts or osteoclasts [59–61]. In standard cell cultures, known to be Se-deficient conditions [62], Se supplementation in human fetal osteoblast (hFOB) cells restored GPx and TrxR activities [63]. Likewise, Se supplementation in primary bone marrow stromal cells (BMSCs) that are able to differentiate into mesenchymal cells such as osteoblasts also increased GPx and TrxR activities (Fig. 1B), consequently reducing intracellular ROS levels and DNA damage [60] and counteracting hydrogen peroxide-suppressed osteoblastic differentiation [64].

2.1. Synergistic effect of vitamin D and Se on TrxR in osteoblasts

Basal steady state TrxR1 mRNA is regulated by transcriptional factor Oct-1 and SP1/SP3, which bind the core promoter of housekeeping gene *TXNRD1* encoding TrxR1 mRNA [65]. Inducible TrxR1 mRNA is regulated by a transcriptional factor termed Nrf2 that binds to the antioxidant response element promoter of the *TXNRD1* gene [66]. Post-transcriptional regulation of TrxR by Se at a translational level has been well characterized [20,66,67]. Compounds that are able to stimulate the transcription of TrxR1 mRNA have the potential to generate a synergistic effect with Se on TrxR1 biosynthesis [67–70]. The hormonal form of vitamin D, 1α,25-dihydroxyvitamin D3 (1α,25(OH)2D3), plays an important role in promoting cellular differentiation [71]. In THP-1 monocytic leukemia cells, 1α,25(OH)2D3 and Se synergistically elevated TrxR1 protein and activity through a concerted regulation of transcription and translation by 1α,25(OH)2D3 and Se, respectively [72]. Compared with other 1α,25(OH)2D3-induced genes such as osteocalcin or osteopontin (OPN), the immediate early response of TrxR1 mRNA steady state levels to 1α,25(OH)2D3 exhibits a fast kinetics feature, i.e., maximal elevation was achieved only after 1 h and decline to basal levels occurred within the next several hours in hFOB cells [73]. Such a transient phenomenon is attributed to the presence of several reiterated AUUUA sequence stretches within the 3′ untranslated region of TrxR1 [65], because AUUUA-rich sequences usually endow mRNAs with a rapid degradation feature [74]. In hFOB cells cultured in Se-deficient media, 1α,25(OH)2D3 treatment did not increase TrxR activity, although it up-regulated TrxR1 mRNA; on the contrary, Se supplementation at a concentration that significantly increased TrxR activity did not affect TrxR1 mRNA synthesis, whereas the co-treatment of 1α,25(OH)2D3 and Se synergistically elevated TrxR1 protein and activity (Fig. 1C) [63], thereby suggesting that 1α,25(OH)2D3-mediated osteoblastic differentiation and/or maintenance of the differentiation program would be impaired if Se is deficient in bone.

2.2. GPx and TrxR in osteoclasts

A mounting body of evidence demonstrates that excessive amounts of ROS promote osteoclastogenesis [54,55]. In osteoclasts, among various antioxidant proteins, including superoxide dismutase 1–3, glutaredoxin 1 and 2, TrxR, Trx, GPx1–4, catalase, peroxiredoxin 1–6 as well as the catalytic and regulatory subunit of γ-glutamyl cysteine synthetase, Lean et al. found that the expression of Sec-containing GPx4 mRNA exceeded those of other species except another Sec-containing protein, GPx1, which was an order of magnitude higher than that of GPx4 [58]. GPx is primarily responsible for the degradation of hydrogen peroxide, which has been recognized as a major culprit for promoting osteoclastogenesis. RANKL-induced differentiation of the RAW264.7 murine macrophage cell line toward an osteoclastic phenotype involves NFκB activation. Both NFκB activation and osteoclastic differentiation in response to RANKL were abolished in RAW264.7 cells transfected with a GPx1 expression construct [58,75]. Likewise, although ebselen, an organic selenium compound with GPx-like activity, does not increase intracellular GPx activity [76,77], it pronouncedly inhibits RANKL-induced osteoclastic differentiation [75,78]. Coincidentally, the mechanism of action of estrogen, a well-documented endogenous inhibitor of osteoclastogenesis, involves GPx1 up-expression in osteoclasts [58]. Paradoxically, RANKL, which potently promotes osteoclastic differentiation, also induces GPx1 expression in osteoclasts [58]. RANKL-induced GPx1 expression could be viewed as a negative feedback auto-regulatory mechanism [58] in a manner similar to RANKL-induced interferon-β, which suppresses RANKL-induced expression of c-Fos, an essential transcription factor for osteoclastogenesis [79]. Within a cell, there exists a strict hierarchy governing the response of selenoproteins to Se deficiency, with certain selenoproteins synthesized at the expense of others [80–82]. GPx1 is sensitive to Se deficiency and TrxR1 is relatively resistant to Se deficiency; as a result, modest Se deficiency usually leads to a large reduction of GPx activity and little alteration of TrxR activity [83,84]. The fact that GPx1 is deposited at an overwhelmingly predominant level in osteoclasts from the viewpoint of antioxidant proteins emphasizes the importance of Se availability in inhibiting osteoclastogenesis. However, the impact of Se on this is not as straightforward, since it also increases TrxR that presumably imparts a bidirectional influence on osteoclastogenesis [85,86].

Trx1 in conjunction with TrxR1 not only act as antioxidant proteins in the cytoplasm and inhibit NFκB activation but also function as promoting factors of NFκB activation in the nucleus [85]. The DNA-binding activity of transcriptional factors AP-1, NFκB, and nuclear factor of activated T cells (NFAT), essential for osteoclastic differentiation, relies on Trx to reduce the conserved Cys residues within their DNA-binding domains [75,85,87]. AP-1-, NFκB-, and NFAT-reporter gene expression as well as osteoclast formation were enhanced by RANKL in RAW264.7 cells transfected with a Trx expression construct [75]. Over-expression of Trx-binding protein 2 (TBP2), a negative regulator of Trx [88], in colony-forming unit-granulocyte macrophage precursors substantially suppressed macrophage colony-stimulating factor and RANKL together induced Trx1 expression and osteoclastogenesis [78]. Likewise, over-expression of TBP2 in RAW264 cells also pronouncedly inhibited osteoclast formation in response to RANKL treatment [89]. Consistently, D-allose, a rare sugar that was able to increase TBP2 expression in RAW264.7 cells, suppressed RANKL-induced activation of AP-1, NFκB, and NFAT as well as osteoclastic differentiation [89]. As a key reductase of Trx1, it could be envisioned that TrxR1 promotes the

activation of redox-sensitive transcriptional factors; indeed, overexpression of TrxR1 enhanced NFκB activation and the expression of NFκB-targeted pro-inflammatory genes [90]. What is more, TrxR is able to facilitate NFκB-mediated gene expression independent of the DNA-binding regulation and all earlier steps in the activation pathway [86]. The cascade of TNFα-stimulated NFκB activation from the degradation of IκBα in the cytoplasm to DNA binding in the nucleus as well as NFκB redox status was not influenced by TrxR inhibition through TrxR-specific inhibitors or siRNA knockdown, but these inhibitory measures dramatically reduced NFκB-mediated gene expression, suggesting that TrxR reduces the transactivation potential of NFκB [86]. Altogether, these lines of evidence unveil the possibility of modulating osteoclastogenesis via Trx and TrxR.

Taking both GPx and TrxR into account, the impact of Se that boosts the effect of either of the two on osteoclastic differentiation appears to remain inconclusive. However, animal studies and epidemiologic investigations have shown that whole selenoprotein deletion or Se deficiency is implicated in bone disorders (to be discussed in the next two paragraphs). On the other hand, a compound with the capacity of both increasing GPx activity and suppressing TrxR activity during osteoclastic differentiation would be a promising candidate to be developed for inhibiting abnormal osteoclastogenesis. Plant-derived curcumin, which has been recognized as a new paradigm for the treatment of osteoarthritis [91], lends credence to this hypothesis. Curcumin could protect as effectively as estrogen against ovariectomy-induced bone loss [92]. Curcumin, known as a potent TrxR inhibitor [93–95], dramatically suppressed RANKL-induced osteoclastic differentiation and NFκB activation in RAW264.7 cells [96,97]. Importantly, RANKL-induced GPx1 mRNA and activity in osteoclast precursor cells were enhanced by curcumin [98]. In addition, this hypothesis also appears to be supported by data on gold. On the one hand, gold nanoparticles significantly augmented RANKL-induced GPx1 mRNA and activity as well as suppressed RANKL-induced osteoclastic differentiation and NFκB activation in bone marrow-derived macrophages [99]. On the other hand, gold-derived compounds including auranofin, aurothioglucose, and aurothiomalate exhibited an extraordinary TrxR inhibitory activity at low nanomolar concentrations [100–103], whereby they suppressed osteoclastic bone resorption [104,105].

3. Selenoprotein knockout or biosynthesis impairment

Selenoprotein P (SePP) is a unique Sec-rich protein wherein the larger N-terminal domain has one Sec residue in the redox motif and unusually, the smaller C-terminal domain contains nine Sec residues [106]. Over 60% of the whole plasma Se level is contributed by SePP in Se-replete rats [107]. Plasma SePP is mainly secreted from the liver [108]. Hepatic biosynthesis of SePP has a salient influence on whole-body Se levels [109,110]. The principal roles of SePP are Se transport and storage, being essential for Se homeostasis and distribution [106]. The entry of circulating SePP into a cell is regulated by a receptor-mediated mechanism. The deletion of apolipoprotein receptor 2 or the absence of a functional lipoprotein megalin receptor impaired SePP uptake [111–115]. Under the conditions of Se deficiency, Se storage in different tissues exhibits a hierarchy-dependent retention with brain, endocrine, and reproductive organs ranking the highest and being resistant to Se deficiency [116–118]. Similar to those tissues that are preferentially supplied with Se under Se-deficient conditions, bone was recently found to be a prior target tissue of SePP, thus implying that Se plays a vital role in bone physiology [61,119]. Of the two SePP receptors, lipoprotein megalin receptor was not found in bone, whereas apolipoprotein receptor 2 (APOER2) expression was significantly influenced by SePP levels in a negative feedback manner, suggesting that Se levels in the bone are tightly regulated [61,119]. Indeed, genetic ablation of SePP resulted in a 25-fold drastic reduction of serum Se concentrations but only a 2.5-fold mild decrease of bone Se levels [61]. SePP knockout has been employed for mimicking Se deficiency in tissues highly resistant to Se deprivation [106,111,120]. SePP knockout male mice fed a regular diet suffered from Se loss in the developing bone, and consequently had a reduced ratio of femoral trabecular bone volume (BV) to tissue volume (TV) compared with wild-type male mice [121]. Sec-tRNA$^{[Ser]Sec}$, encoded by *Trsp*, is required for the incorporation of Sec residues into all selenoproteins. Global *Trsp* gene removal is embryonic lethal, whereas conditional *Trsp* knockout in a specific tissue provides a useful tool for studying the role of selenoproteins [122,123]. Using the conditional gene deletion approach to remove the *Trsp* gene from skeletal progenitor cells (osteo-chondroprogenitors), Downey et al. found that the mutant mice exhibited dwarfism, impaired skeletal growth and endochondral bone formation, delayed ossification, and severe auricular chondronecrosis [124], thereby indicating that the preservation of selenoproteins in bone is essential for normal skeletal development and implying that severe Se deficiency is detrimental to bone.

Thyroid hormones participate in regulating skeletal development and growth via promoting anabolic actions, and accordingly thyroid hormone metabolism dysfunction during childhood causes delayed bone maturation and linear growth [125]. Se modulates hormone axis via Sec-dependent proteins Dio1, 2, and 3, which catalyze the reductive elimination of iodide from iodothyronines. Dio1 and 2 convert the hormone precursor 3,3′,5,5′-tetraiodothyronine (T4) into the active hormone, 3,3′,5-triiodothyronine (T3). Conversely, Dio3 converts T4 and T3 into inactive metabolites, 3,3′,5′-triiodothyronine (rT3) and 3,3′-diiodothyronine, respectively [126]. Therefore, Se deficiency and/or impairment of selenoprotein biosynthesis machinery would cause thyroid axis derangement and consequently a thyroid hormone-responsive delay of bone development. In this regard, a convincing direct link has been established in humans. Children with homozygous or compound heterozygous mutations in SBP2, a key trans-acting factor for the co-translational insertion of Sec into selenoproteins, had abnormal thyroid function tests (high serum T4 and rT3 and low serum T3) along with the syndromes of growth retardation and delayed bone maturation [127–129]. Serum GPx activities and SePP and Se levels as well as Dio2 and GPx activities in skin fibroblasts were reduced in SBP2 defect subjects [127–131]. Combined treatment of T3 and growth hormone nearly normalized the thyroid function tests and significantly improved longitudinal bone growth and maturation in a short stature Japanese boy with the SBP2 mutation [131], whereas Se supplementation by using Se-rich yeast in the individuals with inherited partial SBP2 deficiency failed to restore thyroid hormone metabolism dysfunction or increase GPx activity although it increased serum Se concentrations [130]. Overall, the syndrome of growth retardation and delayed bone maturation involved in SBP2 defective individuals highlights the importance of selenoproteins for bone development.

4. Se deficiency

4.1. Skeletal development

Cao et al. reported that Se deprivation in first-generation mice that only had approximately 10% of normal hepatic Se levels and GPx activities augmented osteoclastic activity and bone resorption, as indicated by significantly reduced trabecular number and the ratio of BV to TV, as well as significantly increased trabecular separation, serum intact parathyroid hormone, and tartrate-resistant acid phosphatase (TRAP) [132]. Moreno-Reyes et al. showed that continuous Se deprivation up to second-generation rats that only had approximately 1–2% of normal plasma Se levels and erythrocyte GPx activities resulted in growth retardation and impaired skeletal development, as evidenced by thin trabecular bone architecture, reduced trabecular bone volume/surface, low bone mineral density (BMD) and urinary deoxypyridinoline, and high plasma intact parathyroid hormone and urinary calcium [133].

4.2. Kashin–Beck disease (KBD)

KBD, endemic in certain areas of the world, is a chronic and degenerative osteoarthropathy with the symptoms of skeletal and joint deformations, short limb and dwarfism, and joint destruction, enlargement, and pain [134–138]. Most KBD cases were found in Se-deficient districts [138–140]. In the Tibet Autonomous Region, one of the most prevalent areas of KBD in China, plasma Se levels in 90% of the affected children and a third of the affected children were lower than 27 ng/mL and 5 ng/mL, respectively [139], whereas optimal plasma Se concentrations for achieving maximal GPx activity are 80–100 ng/mL [141–144]. Therefore, Se deficiency has been regarded as a putative risk factor of KBD. This notion is further corroborated by: 1) genetic evidence showing that selenoprotein knockout from osteo-chondroprogenitors phenotypically replicated many pathological features of KBD in mice [124]; 2) that a KBD rat model can be induced by T-2 toxin exposure and a low-nutrition diet in which Se is deficient [145]; and 3) the partial protective effects of Se supplementation against the KBD syndrome [146,147].

4.3. Osteoporosis

Osteoporosis usually occurs in the elderly, with a high prevalence in postmenopausal women. This disease is characterized by bone loss and fragile porous bones that lead to an increased risk of fractures. In osteoporosis, bone loss results from disturbed equilibrium between osteoblastic bone formation activities and osteoclastic bone resorption [148]. It has been well documented that excess amounts of ROS or reduced estrogen levels increase osteoclast number and bone resorption [54]. An association between ROS elevation and estrogen reduction in bone marrow has been noted [54]. The GSH system, comprising NADPH, GSH, and glutathione reductase, and the Trx system, composed of NADPH, Trx, and TrxR, play a crucial role in antioxidant defense in concert because the two systems reciprocally provide electrons to constitute a functional backup for each other [149–151]. Many recent studies provide evidence that simultaneous inhibition of both Trx and GSH systems greatly enhances oxidative stress compared with single-system inhibition [152–156]. Unfortunately, estrogen deficiency after ovariectomy not only resulted in the simultaneous impairment of GSH and Trx systems [157], but also compromised other antioxidant enzymes, including GPx and superoxide dismutase, in the bone marrow of rats [158]. Nonetheless, exogenous antioxidant supplementation using N-acetyl cysteine, ascorbate, or pegylated catalase abolished ovariectomy-induced bone loss [58,158]. Therefore, Se deficiency that compromises the biosynthesis of a number of antioxidant selenoenzymes would evoke and/or aggregate osteoporosis [159]. Such an assumption is supported by two population-based studies. The first was a prospective study, which characterized the association between Se status and bone mass among healthy euthyroid postmenopausal women, demonstrating that plasma Se levels or SePP concentrations were positively correlated with hip and lumbar spine BMD at study entry as well as after the 6-year follow-up [160]. The second was a case–control study, which investigated the link between antioxidant intake and the risk of osteoporotic hip fracture and whether the link was modified by cigarette smoking, commonly known as a risk factor of osteoporotic hip fracture [161], revealing an inverse dose–response association between Se intake and hip fracture risk among ever smokers, with a 73% lower risk when the highest and lowest quintiles of Se intake were compared [162].

5. Rheumatoid arthritis

5.1. Se at supranutritional dose levels suppresses NFκB activity

Rheumatoid arthritis is a chronic autoimmune disease that affects synovial tissue in multiple joints. Compelling evidence shows that the activation of NFκB in the synovium is a hallmark of rheumatoid arthritis, and blockade of NFκB activation is an effective strategy of preventing against irreversible damage to the adjacent cartilage and bone [163–169]. Excessive amounts of ROS promote NFκB activation in the cytoplasm, whereas maintaining Cys residues within the DNA-binding domain of NFκB in the reducing thiol form is essential for NFκB activation in the nucleus. The compartmentally contrasting redox modulation in the cascade of NFκB activation renders either antioxidants or pro-oxidants likely to inhibit NFκB activation. In the cytoplasm, GPx1, TrxR1, and other selenoproteins with antioxidant attributes together inhibit NFκB activation via neutralizing ROS and increasing the production of arachidonic acid-derived 15-deoxy-Δ12,14-prostaglandin J2, an endogenous inhibitor of IκB kinase β [170,171]. However, in the nucleus, Trx1 in conjugation with TrxR1 enhance the DNA-binding capacity of NFκB [85,90], and TrxR1 reduces the transactivation potential of NFκB [86]. The action of Se at low essential levels (normally 0.1 μM selenite in cultured cells), which are required for sustaining the full activity of a battery of selenoproteins in NFκB activation is, therefore, a tricky issue owing to the presence of TrxR [172]. However, at tolerable high-dose levels that do not trigger perceived cytotoxicity (2–5 μM selenite for certain types of cell lines), selenite readily reacts with thiol groups in proteins, leading to the formation of the selenotrisulfide type of adduct [46]. This unique pro-oxidant property of Se compounds and their metabolites endows Se with an unambiguous capacity to suppress the DNA-binding activity of NFκB in the nucleus [173]. In RAW264.7 cells, whose selenoenzymes could be saturated by 0.1 μM selenite [171], 2 μM selenite that had no cytotoxicity substantially suppressed lipopolysaccharide-induced NFκB activation and its downstream gene expression, such as inducible nitric oxide synthase [33] and cyclooxygenase-2 [34]. It should be noted that these Se concentrations employed in cell culture systems should be considered as pharmacological levels that can be achieved only through supranutritional Se administration in vivo. Consistently, Se at tolerable high-dose levels suppressed carcinogen- and allergen-induced NFκB activation in rats and mice, respectively [30,32]. Recently, in an antigen-induced arthritis model in mice, Vieira et al. showed that short-term intake of high-dose Se for 7 days from a diet containing 9.4 ppm Se in the form of Se-yeast, which otherwise would be toxic if consumed for a longer period, significantly reduced the inflammatory cells recruited to the knee cavity and peri-articular proinflammatory cytokines, such as TNFα, IL1β, and CXCL1. In an adjuvant-induced arthritis model in rats, they also found that the same Se treatment for 10 days significantly reduced paw edema, hypernociception, and peri-articular neutrophil influx, TNFα, IL1β, and IL-10. In an ex vivo experiment using macrophages isolated from mice treated with or without 9.4 ppm Se, they demonstrated that the Se treatment inhibited lipopolysaccharide-stimulated production of TNFα and CXCL1 [174]. Currently, the idea of using pro-oxidative activities of supraphysiological selenite has just been challenged because such an approach is not successful in postoperative critically ill patients with severe sepsis [175,176]. Therefore, a more appropriate clinical study would be to determine whether a given rheumatoid arthritis patient has developed a severe Se deficit, and then to suggest a personalized supplementation regimen aiming at achieving optimal Se levels in blood to optimize selenoprotein P expression.

5.2. TrxR as a drug target of rheumatoid arthritis

Rheumatoid arthritis has higher levels of Trx and TrxR in the synovial fluid and cells compared with osteoarthritis [177–180]. Trx enhanced NFκB activation and pro-inflammatory cytokine production in rheumatoid synovial fibroblasts subjected to TNFα treatment [178], implying that Trx and TrxR in the synovial fluid and cells aggravate rheumatoid inflammation [177,178]. Gold-derived auranofin and aurothioglucose are robust TrxR inhibitors [100–103], and they have been extensively employed for treating rheumatoid arthritis for more than two decades [181]. The coincident linkage of an abnormally up-regulated Trx system

and a widely used therapeutic agent with a powerful TrxR inhibitory activity in the case of rheumatoid arthritis supports the notion that TrxR is a prime drug target of rheumatoid arthritis.

6. Breast cancer

6.1. Vicious cycle

Bone metastasis occurs frequently in advanced breast cancer patients [182]. Metastatic breast cancer cells can induce an osteoblastic inflammatory response. The resultant pro-inflammatory cytokines then spur osteoclastic differentiation, leading to bone matrix degradation and concomitant growth factor leakage into the bone microenvironment. The released growth factors, such as transforming growth factor β, vascular endothelial growth factor, and insulin-like growth factors, in turn promote the proliferation of metastatic breast cancer cells and the establishment of metastatic tumors [182,183]. The crosstalk between metastatic breast cancer cells, osteoblasts, and osteoclasts results in a vicious cycle that is more and more affable to bone tumors and finally brings about osteolysis [182,183]. An approach that can impair one or more steps in the cascade of the vicious cycle would attenuate osteolytic lesions. Chen et al. showed that human breast cancer cell-conditioned media activated osteoblastic NFκB, resulting in the up-regulation of pro-inflammatory cytokines and enzymes, including interleukin 6, monocyte chemoattractant protein 1, cyclooxygenase 2, and inducible nitric oxide synthase; however, all these osteoblast inflammatory stress responses could be substantially suppressed by Se at high-dose levels that did not trigger cytotoxicity [184], suggesting that supranutritional Se supplementation in breast cancer patients would diminish the vicious cycle.

In addition, OPN, a secreted protein present in tissues and bodily fluids, also plays a role in promoting the vicious cycle [183,185]. Osteoclastogenesis does not occur in the absence of OPN [186–188]. In contrast, exogenous addition of OPN greatly increased RANKL expression and significantly reduced OPG expression in stromal cells; the elevated ratio of RANKL to OPG promoted osteoclastic differentiation [185]. OPN is over-expressed in breast cancer cells [183,185,189], which, after metastasis to the skeleton, enhances OPN expression in osteoblasts [190]. Therefore, metastatic breast cancer patients usually have a high level of circulating OPN [189,191]. The impact of Se on OPN expression has not yet been systematically elucidated. Several separated studies have hinted that Se may act as a negative regulator of OPN expression. Chen et al. and Serwin et al. found plasma concentrations of OPN and Se to be significantly increased and reduced in psoriasis patients, respectively [192,193]. Kadry and Rashed confirmed these findings and indicated that there existed a strong negative association between plasma Se and OPN among psoriasis patients [194]. Se supplementation down-regulated mRNA levels of Runx2, a transcriptional factor responsible for OPN expression, in vascular smooth muscle cells [195,196]. Importantly, OPN expression in breast cancer cells exposed to high-dose Se was largely reduced, and OPN expression in mammary tumors in mice that received supranutritional Se was markedly inhibited [197]. Taking the metastasis-promoting function of OPN into account [198–200], supranutritional Se supplementation in breast cancer patients would help to dampen the vicious cycle via reducing the metastatic potential of breast cancer cells [201,202]. In this regard, it remains of interest to elucidate the influences of Se on OPN expression in osteoblasts and osteoclasts.

6.2. Aromatase inhibitor

After menopause, estrogen mainly results from the aromatization of androgen precursors in adipose tissue. Postmenopausal women with breast cancer usually undergo aromatase inhibitor therapy to reduce estrogen that promotes breast carcinoma development; however,

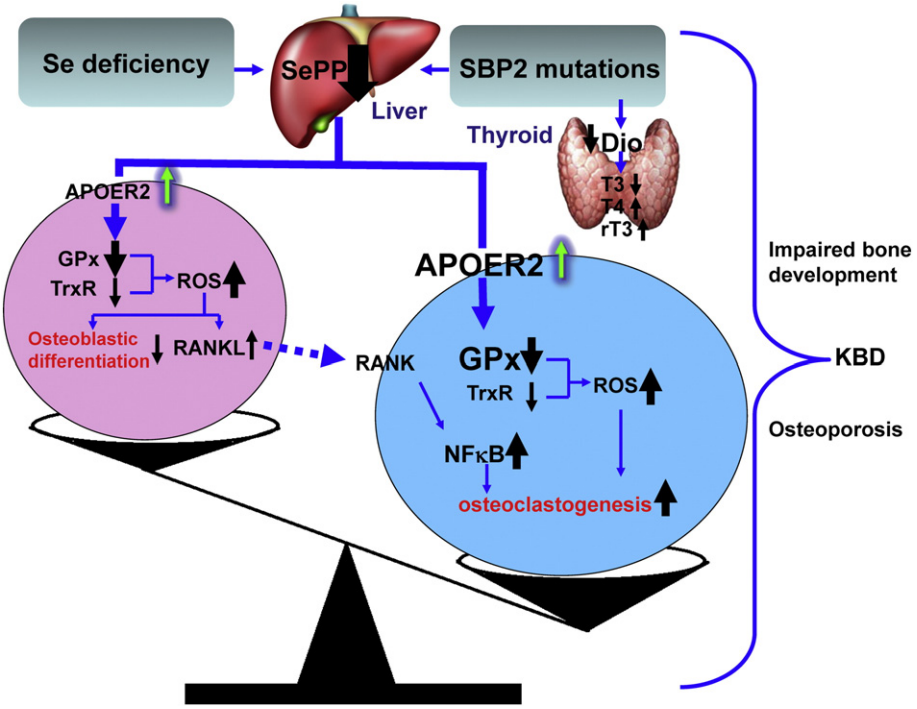

Fig. 2. Influences of Se deficiency and impaired selenoprotein biosynthesis machinery on bone development and maintenance. The entry of circulating SePP into a cell is regulated by a receptor-mediated mechanism. Hepatic biosynthesis of SePP has a salient influence on whole-body Se levels. APOER2 as a SePP receptor of bone is significantly influenced by SePP levels in a negative feedback manner, suggesting that Se levels in the bone are tightly regulated. Nonetheless, severe Se deficiency is still able to cause Se deficits in bones. GPx1 is sensitive to Se deficiency and TrxR1 is relatively resistant to Se deficiency due to the selenoprotein hierarchy that governs the response of various selenoproteins to Se deficiency. Impaired selenoprotein biosynthesis increases intracellular ROS levels. Excessive amounts of ROS suppress osteoblastic differentiation and promote osteoclastic differentiation along with NFκB activation independently. Moreover, ROS stimulates RANKL expression in osteoblasts and acts as a crucial intracellular signal mediator for RANKL-stimulated osteoclastic differentiation. In addition to Se deficiency, SBP2 deficiency also reduces selenoprotein biosynthesis including SePP and Dio; accordingly the syndromes of growth retardation and delayed bone maturation along with thyroid axis derangement in children carrying SBP2 mutations have been identified.

estrogen also plays an important role in maintaining bone health, and postmenopausal women are liable to lose their bone mass due to the decline of estrogen. In this situation, aromatase inhibitor treatments predisposed postmenopausal women to an increased risk of osteoporosis and fracture [203–205]. In a rat model employing anastrozole, a clinically used aromatase inhibitor, to deplete estrogen and consequently evoke bony deterioration, as indicated by significant elevation of serum TRAP activity, intraperitoneal injection of elemental Se nanoparticles at a dose of 1.0 mg/kg for 1 week significantly reversed serum TRAP activity to normal levels [206]. Consistently, in an ovariectomized rat model, the same Se treatment also significantly reduced serum TRAP activity vis-à-vis the model alone [206]. The used Se dose could be viewed as a high but still safe level since we observed that the same Se treatment in mice did not cause perceived toxicity, whereas overt toxicity would occur at double the dose (unpublished data). The underlying mechanisms likely involve the suppression of NFκB activation through selenoprotein biosynthesis and/or the accumulation of low-molecular weight Se metabolites that can readily react with thiol groups [45–48, 173]. Anyway, these results suggest that supranutritional Se supplementation in breast cancer patients who receive aromatase inhibitor therapy is helpful for reducing the risk of osteoporosis and fracture.

7. Conclusion

Removing the *Trsp* gene that encodes Sec-tRNA$^{[Ser]Sec}$, which is required for Sec incorporation into selenoproteins, from skeletal progenitor cells impairs skeletal development. Mutations of SBP2, which are essential for Sec insertion into selenoproteins, cause growth retardation and delayed bone maturation in children probably through thyroid axis derangement due to impaired Dio enzymatic activities. Knockout of SePP, which is responsible for Se transport and local Se storage, evokes bone loss. These findings collectively demonstrate that the preservation of selenoproteins in bone is essential to normal skeletal development. On the one hand, selenoprotein biosynthesis is compromised under Se-deficient status; on the other hand, Se levels in the bone under the condition of lower peripheral SePP levels are more effectively preserved via a distinct negative feedback increase of APOER2 that mediates SePP entry into bone cells. Nonetheless, excessive or severely inadequate Se intake still results in poor bone development and low BMD. The influences of Se levels and selenoprotein biosynthesis on osteoblastic and osteoclastic differentiation as well as consequent reciprocal interaction between osteoblasts and osteoclasts are summarized in Fig. 2. Finally, the health benefits and risks of modest excessive amounts of Se supplementation exceeding the requirements for selenoprotein biosynthesis in individuals with normal physiological functions remain controversial according to several lines of emerging evidence [207–209]. Therefore, disease-free individuals are advised to maintain an optimal Se intake that neither exceeds nor is lower than the requirements for selenoprotein biosynthesis.

Conflict of interest

All authors state that they have no conflicts of interest.

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References

[1] Z.R. Stoytcheva, M.J. Berry, Transcriptional regulation of mammalian selenoprotein expression, Biochim. Biophys. Acta 1790 (2009) 1429–1440.
[2] M.A. Reeves, P.R. Hoffmann, The human selenoproteome: recent insights into functions and regulation, Cell. Mol. Life Sci. 66 (2009) 2457–2478.
[3] J. Lu, A. Holmgren, Selenoproteins, J. Biol. Chem. 284 (2009) 723–727.
[4] S. Gromer, J.K. Eubel, B.L. Lee, J. Jacob, Human selenoproteins at a glance, Cell. Mol. Life Sci. 62 (2005) 2414–2437.
[5] J. Donovan, P.R. Copeland, Threading the needle: getting selenocysteine into proteins, Antioxid. Redox Signal. 12 (2010) 881–892.
[6] D.L. Hatfield, B.A. Carlson, X.M. Xu, H. Mix, V.N. Gladyshev, Selenocysteine incorporation machinery and the role of selenoproteins in development and health, Prog. Nucleic Acid Res. Mol. Biol. 81 (2006) 97–142.
[7] E.S. Arnér, Selenoproteins—what unique properties can arise with selenocysteine in place of cysteine? Exp. Cell Res. 316 (2010) 1296–1303.
[8] R.J. Hondal, E.L. Ruggles, Differing views of the role of selenium in thioredoxin reductase, Amino Acids 41 (2011) 73–89.
[9] G.W. Snider, E. Ruggles, N. Khan, R.J. Hondal, Selenocysteine confers resistance to inactivation by oxidation in thioredoxin reductase: comparison of selenium and sulfur enzymes, Biochemistry 52 (2013) 5472–5481.
[10] R. Koishi, T. Nakamura, T. Takazawa, C. Yoshimura, N. Serizawa, Production of functional human selenocysteine-containing KDRF/thioredoxin reductase in *E. coli*, J. Biochem. 127 (2000) 977–983.
[11] S. Bar-Noy, S.N. Gorlatov, T.C. Stadtman, Overexpression of wild type and SeCys/Cys mutant of human thioredoxin reductase in *E. coli*: the role of selenocysteine in the catalytic activity, Free Radic. Biol. Med. 30 (2001) 51–61.
[12] L. Schomburg, U. Schweizer, J. Köhrle, Selenium and selenoproteins in mammals: extraordinary, essential, enigmatic, Cell. Mol. Life Sci. 61 (2004) 1988–1995.
[13] J.R. Arthur, The glutathione peroxidases, Cell. Mol. Life Sci. 57 (2000) 1825–1835.
[14] R. Brigelius-Floh, Tissue-specific functions of individual glutathione peroxidases, Free Radic. Biol. Med. 27 (1999) 951–965.
[15] R. Brigelius-Flohé, Glutathione peroxidases and redox-regulated transcription factors, Biol. Chem. 387 (2006) 1329–1335.
[16] X.G. Lei, Glutathione peroxidase-1 gene knockout on body antioxidant defense in mice, Biofactors 14 (2001) 93–99.
[17] E.S. Arnér, Focus on mammalian thioredoxin reductases—important selenoproteins with versatile functions, Biochim. Biophys. Acta 1790 (2009) 495–526.
[18] A. Holmgren, Antioxidant function of thioredoxin and glutaredoxin systems, Antioxid. Redox Signal. 2 (2000) 811–820.
[19] E.S. Arnér, A. Holmgren, Physiological functions of thioredoxin and thioredoxin reductase, Eur. J. Biochem. 267 (2000) 6102–6109.
[20] A.K. Rundlöf, E.S. Arnér, Regulation of the mammalian selenoprotein thioredoxin reductase 1 in relation to cellular phenotype, growth, and signaling events, Antioxid. Redox Signal. 6 (2004) 41–52.
[21] J. Nordberg, E.S. Arnér, Reactive oxygen species, antioxidants, and the mammalian thioredoxin system, Free Radic. Biol. Med. 31 (2001) 1287–1312.
[22] J. Lu, A. Holmgren, Thioredoxin system in cell death progression, Antioxid. Redox Signal. 17 (2012) 1738–1747.
[23] M.V. Kasaikina, D.L. Hatfield, V.N. Gladyshev, Understanding selenoprotein function and regulation through the use of rodent models, Biochim. Biophys. Acta 1823 (2012) 1633–1642.
[24] C.B. Allan, G.M. Lacourciere, T.C. Stadtman, Responsiveness of selenoproteins to dietary selenium, Annu. Rev. Nutr. 19 (1999) 1–16.
[25] K.M. Brown, J.R. Arthur, Selenium, selenoproteins and human health: a review, Public Health Nutr. 4 (2001) 593–599.
[26] H. Zeng, J.J. Cao, G.F. Combs Jr., Selenium in bone health: roles in antioxidant protection and cell proliferation, Nutrients 5 (2013) 97–110.
[27] J.M. Park, A. Kim, J.H. Oh, A.S. Chung, Methylseleninic acid inhibits PMA-stimulated pro-MMP-2 activation mediated by MT1-MMP expression and further tumor invasion through suppression of NF-kappaB activation, Carcinogenesis 28 (2007) 837–847.
[28] M.J. Christensen, E.T. Nartey, A.L. Hada, R.L. Legg, B.R. Barzee, High selenium reduces NF-kappaB-regulated gene expression in uninduced human prostate cancer cells, Nutr. Cancer 58 (2007) 197–204.
[29] S. Jüliger, H. Goenaga-Infante, T.A. Lister, J. Fitzgibbon, S.P. Joel, Chemosensitization of B-cell lymphomas by methylseleninic acid involves nuclear factor-kappaB inhibition and the rapid generation of other selenium species, Cancer Res. 67 (2007) 10984–10992.
[30] N.Y. Alwahaibi, S.B. Budin, J. Mohamed, A. Alhamdani, Nuclear factor-kappa B as a promising target for selenium chemoprevention in rat hepatocarcinogenesis, J. Gastroenterol. Hepatol. 25 (2010) 786–791.
[31] F. Zhang, W. Yu, J.L. Hargrove, P. Greenspan, R.G. Dean, E.W. Taylor, D.K. Hartle, Inhibition of TNF-alpha induced ICAM-1, VCAM-1 and E-selectin expression by selenium, Atherosclerosis 161 (2002) 381–386.
[32] D.W. Jeong, M.H. Yoo, T.S. Kim, J.H. Kim, I.Y. Kim, Protection of mice from allergen-induced asthma by selenite: prevention of eosinophil infiltration by inhibition of NF-kappa B activation, J. Biol. Chem. 277 (2002) 17871–17876.
[33] K.S. Prabhu, F. Zamamiri-Davis, J.B. Stewart, J.T. Thompson, L.M. Sordillo, C.C. Reddy, Selenium deficiency increases the expression of inducible nitric oxide synthase in RAW 264.7 macrophages: role of nuclear factor-kappaB in up-regulation, Biochem. J. 366 (2002) 203–209.
[34] F. Zamamiri-Davis, Y. Lu, J.T. Thompson, K.S. Prabhu, P.V. Reddy, L.M. Sordillo, C.C. Reddy, Nuclear factor-kappaB mediates over-expression of cyclooxygenase-2 during activation of RAW 264.7 macrophages in selenium deficiency, Free Radic. Biol. Med. 32 (2002) 890–897.
[35] J.L. Fischer, E.M. Mihelc, K.E. Pollok, M.L. Smith, Chemotherapeutic selectivity conferred by selenium: a role for p53-dependent DNA repair, Mol. Cancer Ther. 6 (2007) 355–361.
[36] Y.R. Seo, M.R. Kelley, M.L. Smith, Selenomethionine regulation of p53 by a ref1-dependent redox mechanism, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 14548–14553.

[37] S.W. Jeong, H.J. Jung, M.M. Rahman, J.N. Hwang, Y.R. Seo, Protective effects of selenomethionine against ionizing radiation under the modulation of p53 tumor suppressor, J. Med. Food 12 (2009) 389–393.
[38] J.L. Fischer, J.K. Lancia, A. Mathur, M.L. Smith, Selenium protection from DNA damage involves a Ref1/p53/Brca1 protein complex, Anticancer Res. 26 (2006) 899–904.
[39] W.M. El-Sayed, T. Aboul-Fadl, J.G. Lamb, J.C. Roberts, M.R. Franklin, Effect of selenium-containing compounds on hepatic chemoprotective enzymes in mice, Toxicology 220 (2006) 179–188.
[40] H. Xiao, K.L. Parkin, Induction of phase II enzyme activity by various selenium compounds, Nutr. Cancer 55 (2006) 210–223.
[41] D. Wang, E.W. Taylor, Y. Wang, X. Wan, J. Zhang, Encapsulated nanoepigallocatechin-3-gallate and elemental selenium nanoparticles as paradigms for nanochemoprevention, Int. J. Nanomedicine 7 (2012) 1711–1721.
[42] C. Ip, H.J. Thompson, Z. Zhu, H.E. Ganther, In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention, Cancer Res. 60 (2000) 2882–2886.
[43] G.X. Li, H.J. Lee, Z. Wang, H. Hu, J.D. Liao, J.C. Watts, G.F. Combs Jr., J. Lü, Superior in vivo inhibitory efficacy of methylseleninic acid against human prostate cancer over selenomethionine or selenite, Carcinogenesis 29 (2008) 1005–1012.
[44] Z. Wang, C. Jiang, J. Lü, Induction of caspase-mediated apoptosis and cell-cycle G1 arrest by selenium metabolite methylselenol, Mol. Carcinog. 34 (2002) 113–120.
[45] R. Irons, B.A. Carlson, D.L. Hatfield, C.D. Davis, Both selenoproteins and low molecular weight selenocompounds reduce colon cancer risk in mice with genetically impaired selenoprotein expression, J. Nutr. 136 (2006) 1311–1317.
[46] H.E. Ganther, Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase, Carcinogenesis 20 (1999) 1657–1666.
[47] A. Ghose, J. Fleming, K. El-Bayoumy, P.R. Harrison, Enhanced sensitivity of human oral carcinomas to induction of apoptosis by selenium compounds: involvement of mitogen-activated protein kinase and Fas pathways, Cancer Res. 61 (2001) 7479–7487.
[48] G.F. Combs Jr., L.C. Clark, B.W. Turnbull, An analysis of cancer prevention by selenium, Biofactors 14 (2001) 153–159.
[49] W.J. Boyle, W.S. Simonet, D.L. Lacey, Osteoclast differentiation and activation, Nature 423 (2003) 337–342.
[50] K. Matsuo, N. Irie, Osteoclast–osteoblast communication, Arch. Biochem. Biophys. 473 (2008) 201–209.
[51] N.A. Sims, J.H. Gooi, Bone remodeling: multiple cellular interactions required for coupling of bone formation and resorption, Semin. Cell Dev. Biol. 19 (2008) 444–451.
[52] K. Nakahama, Cellular communications in bone homeostasis and repair, Cell. Mol. Life Sci. 67 (2010) 4001–4009.
[53] T. Suda, N. Takahashi, N. Udagawa, E. Jimi, M.T. Gillespie, T.J. Martin, Modulation of osteoclast differentiation and function by the new members of the tumor necrosis factor receptor and ligand families, Endocr. Rev. 20 (1999) 345–357.
[54] S.C. Manolagas, From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis, Endocr. Rev. 31 (2010) 266–300.
[55] F. Wauquier, L. Leotoing, V. Coxam, J. Guicheux, Y. Wittrant, Oxidative stress in bone remodelling and disease, Trends Mol. Med. 15 (2009) 468–477.
[56] X.C. Bai, D. Lu, A.L. Liu, Z.M. Zhang, X.M. Li, Z.P. Zou, W.S. Zeng, B.L. Cheng, S.Q. Luo, Reactive oxygen species stimulates receptor activator of NF-kappaB ligand expression in osteoblast, J. Biol. Chem. 280 (2005) 17497–17506.
[57] N.K. Lee, Y.G. Choi, J.Y. Baik, S.Y. Han, D.W. Jeong, Y.S. Bae, N. Kim, S.Y. Lee, A crucial role for reactive oxygen species in RANKL-induced osteoclast differentiation, Blood 106 (2005) 852–859.
[58] J.M. Lean, C.J. Jagger, B. Kirstein, K. Fuller, T.J. Chambers, Hydrogen peroxide is essential for estrogen-deficiency bone loss and osteoclast formation, Endocrinology 146 (2005) 728–735.
[59] I. Dreher, N. Schütze, A. Baur, K. Hesse, D. Schneider, J. Köhrle, F. Jakob, Selenoproteins are expressed in fetal human osteoblast-like cells, Biochem. Biophys. Res. Commun. 245 (1998) 101–107.
[60] R. Ebert, M. Ulmer, S. Zeck, J. Meissner-Weigl, D. Schneider, H. Stopper, N. Schupp, M. Kassem, F. Jakob, Selenium supplementation restores the antioxidative capacity and prevents cell damage in bone marrow stromal cells in vitro, Stem Cells 24 (2006) 1226–1235.
[61] N. Pietschmann, E. Rijntjes, A. Hoeg, M. Stoedter, U. Schweizer, P. Seemann, L. Schomburg, Selenoprotein P is the essential selenium transporter for bones, Metallomics 6 (2014) 1043–1049.
[62] M. Leist, B. Raab, S. Maurer, U. Rösick, R. Brigelius-Flohé, Conventional cell culture media do not adequately supply cells with antioxidants and thus facilitate peroxide-induced genotoxicity, Free Radic. Biol. Med. 21 (1999) 297–306.
[63] F. Jakob, K. Becker, E. Paar, R. Ebert-Duemig, N. Schütze, Expression and regulation of thioredoxin reductases and other selenoproteins in bone, Methods Enzymol. 347 (2002) 168–179.
[64] H. Liu, W. Bian, S. Liu, K. Huang, Selenium protects bone marrow stromal cells against hydrogen peroxide-induced inhibition of osteoblastic differentiation by suppressing oxidative stress and ERK signaling pathway, Biol. Trace Elem. Res. 150 (2012) 441–450.
[65] A.K. Rundlöf, M. Carlsten, E.S. Arnér, The core promoter of human thioredoxin reductase 1: cloning, transcriptional activity, and Oct-1, Sp1, and Sp3 binding reveal a housekeeping-type promoter for the AU-rich element-regulated gene, J. Biol. Chem. 276 (2001) 30542–30551.
[66] K.J. Hintze, K.A. Wald, H. Zeng, E.H. Jeffery, J.W. Finley, Thioredoxin reductase in human hepatoma cells is transcriptionally regulated by sulforaphane and other electrophiles via an antioxidant response element, J. Nutr. 133 (2003) 2721–2727.
[67] J. Zhang, V. Svehlíková, Y. Bao, A.F. Howie, G.J. Beckett, G. Williamson, Synergy between sulforaphane and selenium in the induction of thioredoxin reductase 1 requires both transcriptional and translational modulation, Carcinogenesis 24 (2003) 497–503.
[68] L.N. Barrera, A. Cassidy, W. Wang, T. Wei, N.J. Belshaw, I.T. Johnson, R. Brigelius-Flohé, Y. Bao, TrxR1 and GPx2 are potently induced by isothiocyanates and selenium, and mutually cooperate to protect Caco-2 cells against free radical-mediated cell death, Biochim. Biophys. Acta 1823 (2012) 1914–1924.
[69] W. Wang, S. Wang, A.F. Howie, G.J. Beckett, R. Mithen, Y. Bao, Sulforaphane, erucin, and iberin up-regulate thioredoxin reductase 1 expression in human MCF-7 cells, J. Agric. Food Chem. 53 (2005) 1417–1421.
[70] L. Campbell, F. Howie, J.R. Arthur, F. Nicol, G. Beckett, Selenium and sulforaphane modify the expression of selenoenzymes in the human endothelial cell line EAhy926 and protect cells from oxidative damage, Nutrition 23 (2007) 138–144.
[71] A. Gurlek, M.R. Pittelkow, R. Kumar, Modulation of growth factor/cytokine synthesis and signaling by 1alpha,25-dihydroxyvitamin D(3): implications in cell growth and differentiation, Endocr. Rev. 23 (2002) 763–786.
[72] N. Schütze, J. Fritsche, R. Ebert-Dümig, D. Schneider, J. Köhrle, R. Andreesen, M. Kreutz, F. Jakob, The selenoprotein thioredoxin reductase is expressed in peripheral blood monocytes and THP1 human myeloid leukemia cells—regulation by 1,25-dihydroxyvitamin D3 and selenite, Biofactors 10 (1999) 329–338.
[73] N. Schütze, M. Bachthaler, A. Lechner, J. Köhrle, F. Jakob, Identification by differential display PCR of the selenoprotein thioredoxin reductase as a 1 alpha,25(OH)2-vitamin D3-responsive gene in human osteoblasts—regulation by selenite, Biofactors 7 (1998) 299–310.
[74] G. Shaw, R. Kamen, A conserved AU sequence from the 3′ untranslated region of GM-CSF mRNA mediates selective mRNA degradation, Cell 46 (1986) 659–667.
[75] J. Lean, B. Kirstein, Z. Urry, T. Chambers, K. Fuller, Thioredoxin-1 mediates osteoclast stimulation by reactive oxygen species, Biochem. Biophys. Res. Commun. 321 (2004) 845–850.
[76] B.K. Sarma, G. Mugesh, Glutathione peroxidase (GPx)-like antioxidant activity of the organoselenium drug ebselen: unexpected complications with thiol exchange reactions, J. Am. Chem. Soc. 127 (2005) 11477–11485.
[77] C.S. Hoefig, K. Renko, J. Köhrle, M. Birringer, L. Schomburg, Comparison of different selenocompounds with respect to nutritional value vs. toxicity using liver cells in culture, J. Nutr. Biochem. 22 (2011) 945–955.
[78] C.J. Aitken, J.M. Hodge, Y. Nishinaka, T. Vaughan, J. Yodoi, C.J. Day, N.A. Morrison, G. C. Nicholson, Regulation of human osteoclast differentiation by thioredoxin binding protein-2 and redox-sensitive signaling, J. Bone Miner. Res. 19 (2004) 2057–2064.
[79] H. Takayanagi, S. Kim, K. Matsuo, H. Suzuki, T. Suzuki, K. Sato, T. Yokochi, H. Oda, K. Nakamura, N. Ida, E.F. Wagner, T. Taniguchi, RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-beta, Nature 416 (2002) 744–749.
[80] M.E. Budiman, J.L. Bubenik, A.C. Miniard, L.M. Middleton, C.A. Gerber, A. Cash, D.M. Driscoll, Eukaryotic initiation factor 4a3 is a selenium-regulated RNA-binding protein that selectively inhibits selenocysteine incorporation, Mol. Cell 35 (2009) 479–489.
[81] J.E. Squires, I. Stoytchev, E.P. Forry, M.J. Berry, SBP2 binding affinity is a major determinant in differential selenoprotein mRNA translation and sensitivity to nonsense-mediated decay, Mol. Cell. Biol. 27 (2007) 7848–7855.
[82] S.C. Low, E. Grundner-Culemann, J.W. Harney, M.J. Berry, SECIS–SBP2 interactions dictate selenocysteine incorporation efficiency and selenoprotein hierarchy, EMBO J. 19 (2000) 6882–6890.
[83] J.C. McCann, B.N. Ames, Adaptive dysfunction of selenoproteins from the perspective of the triage theory: why modest selenium deficiency may increase risk of diseases of aging, FASEB J. 25 (2011) 1793–1814.
[84] S. Wu, K. Sun, X. Wang, D. Wang, X. Wan, J. Zhang, Protonation of epigallocatechin-3-gallate (EGCG) results in massive aggregation and reduced oral bioavailability of EGCG-dispersed selenium nanoparticles, J. Agric. Food Chem. 61 (2013) 7268–7275.
[85] K. Hirota, M. Murata, Y. Sachi, H. Nakamura, J. Takeuchi, K. Mori, J. Yodoi, Distinct roles of thioredoxin in the cytoplasm and in the nucleus. A two-step mechanism of redox regulation of transcription factor NF-kappaB, J. Biol. Chem. 274 (1999) 27891–27897.
[86] J.M. Heilman, T.J. Burke, C.J. McClain, W.H. Watson, Transactivation of gene expression by NF-κB is dependent on thioredoxin reductase activity, Free Radic. Biol. Med. 51 (2011) 1533–1542.
[87] K. Hirota, M. Matsui, S. Iwata, A. Nishiyama, K. Mori, J. Yodoi, AP-1 transcriptional activity is regulated by a direct association between thioredoxin and Ref-1, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 3633–3638.
[88] A. Nishiyama, M. Matsui, S. Iwata, K. Hirota, H. Masutani, H. Nakamura, Y. Takagi, H. Sono, Y. Gon, J. Yodoi, Identification of thioredoxin-binding protein-2/vitamin D(3) up-regulated protein 1 as a negative regulator of thioredoxin function and expression, J. Biol. Chem. 274 (1999) 21645–21650.
[89] K. Yamada, C. Noguchi, K. Kamitori, Y. Dong, Y. Hirata, M.A. Hossain, I. Tsukamoto, M. Tokuda, F. Yamaguchi, Rare sugar D-allose strongly induces thioredoxin-interacting protein and inhibits osteoclast differentiation in Raw264 cells, Nutr. Res. 32 (2012) 116–123.
[90] A. Sakurai, K. Yuasa, Y. Shoji, S. Himeno, M. Tsujimoto, M. Kunimoto, N. Imura, S. Hara, Overexpression of thioredoxin reductase 1 regulates NF-kappa B activation, J. Cell. Physiol. 198 (2004) 22–30.
[91] Y. Henrotin, F. Priem, A. Mobasheri, Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management, Springerplus 2 (2013) 56.
[92] F. Hussan, N.G. Ibraheem, T.A. Kamarudin, A.N. Shuid, I.N. Soelaiman, F. Othman, Curcumin protects against ovariectomy-induced bone changes in rat model, Evid. Based Complement. Alternat. Med. 2012 (2012) 174916.

[93] W. Cai, B. Zhang, D. Duan, J. Wu, J. Fang, Curcumin targeting the thioredoxin system elevates oxidative stress in HeLa cells, Toxicol. Appl. Pharmacol. 262 (2012) 341–348.
[94] J. Fang, J. Lu, A. Holmgren, Thioredoxin reductase is irreversibly modified by curcumin: a novel molecular mechanism for its anticancer activity, J. Biol. Chem. 280 (2005) 25284–25290.
[95] P. Javvadi, L. Hertan, R. Kosoff, T. Datta, J. Kolev, R. Mick, S.W. Tuttle, C. Koumenis, Thioredoxin reductase-1 mediates curcumin-induced radiosensitization of squamous carcinoma cells, Cancer Res. 70 (2010) 1941–1950.
[96] A.C. Bharti, Y. Takada, B.B. Aggarwal, Curcumin (diferuloylmethane) inhibits receptor activator of NF-kappa B ligand-induced NF-kappa B activation in osteoclast precursors and suppresses osteoclastogenesis, J. Immunol. 172 (2004) 5940–5947.
[97] H.J. Moon, W.K. Ko, S.W. Han, D.S. Kim, Y.S. Hwang, H.K. Park, I.K. Kwon, Antioxidants, like coenzyme Q10, selenite, and curcumin, inhibited osteoclast differentiation by suppressing reactive oxygen species generation, Biochem. Biophys. Res. Commun. 418 (2012) 247–253.
[98] W.K. Kim, K. Ke, O.J. Sul, H.J. Kim, S.H. Kim, M.H. Lee, H.J. Kim, S.Y. Kim, H.T. Chung, H.S. Choi, Curcumin protects against ovariectomy-induced bone loss and decreases osteoclastogenesis, J. Cell. Biochem. 112 (2011) 3159–3166.
[99] O.J. Sul, J.C. Kim, T.W. Kyung, H.J. Kim, Y.Y. Kim, S.H. Kim, J.S. Kim, H.S. Choi, Gold nanoparticles inhibited the receptor activator of nuclear factor-κb ligand (RANKL)-induced osteoclast formation by acting as an antioxidant, Biosci. Biotechnol. Biochem. 74 (2010) 2209–2213.
[100] Y. Omata, M. Folan, M. Shaw, R.L. Messer, P.E. Lockwood, D. Hobbs, S. Bouillaguet, H. Sano, J.B. Lewis, J.C. Wataha, Sublethal concentrations of diverse gold compounds inhibit mammalian cytosolic thioredoxin reductase (TrxR1), Toxicol. in Vitro 20 (2006) 882–890.
[101] L. Engman, M. McNaughton, M. Gajewska, S. Kumar, A. Birmingham, G. Powis, Thioredoxin reductase and cancer cell growth inhibition by organogold(III) compounds, Anticancer Drugs 17 (2006) 539–544.
[102] A.D. Smith, C.A. Guidry, V.C. Morris, O.A. Levander, Aurothioglucose inhibits murine thioredoxin reductase activity in vivo, J. Nutr. 129 (1999) 194–198.
[103] S.E. Jackson-Rosario, W.T. Self, Targeting selenium metabolism and selenoproteins: novel avenues for drug discovery, Metallomics 2 (2010) 112–116.
[104] S.J. Vargas, T.G. Jones, M.M. Hurley, L.G. Raisz, Comparison of the effects of auranofin, gold sodium thiomalate, and penicillamine on resorption of cultured fetal rat long bones, J. Bone Miner. Res. 2 (1987) 183–189.
[105] T.J. Hall, H. Jeker, H. Nyugen, M. Schaeublin, Gold salts inhibit osteoclastic bone resorption in vitro, Inflamm. Res. 45 (1996) 230–233.
[106] R.F. Burk, K.E. Hill, Selenoprotein P: an extracellular protein with unique physical characteristics and a role in selenium homeostasis, Annu. Rev. Nutr. 25 (2005) 215–235.
[107] R.F. Burk, K.E. Hill, Selenoprotein P. A selenium-rich extracellular glycoprotein, J. Nutr. 124 (1994) 1891–1897.
[108] K. Renko, M. Werner, I. Renner-Müller, T.G. Cooper, C.H. Yeung, B. Hollenbach, M. Scharpf, J. Köhrle, L. Schomburg, U. Schweizer, Hepatic selenoprotein P (SePP) expression restores selenium transport and prevents infertility and motor-incoordination in Sepp-knockout mice, Biochem. J. 409 (2008) 741–749.
[109] K.E. Hill, J. Zhou, W.J. McMahan, A.K. Motley, J.F. Atkins, R.F. Gesteland, R.F. Burk, Deletion of selenoprotein P alters distribution of selenium in the mouse, J. Biol. Chem. 278 (2003) 13640–13646.
[110] L. Schomburg, U. Schweizer, B. Holtmann, L. Flohé, M. Sendtner, J. Köhrle, Gene disruption discloses role of selenoprotein P in selenium delivery to target tissues, Biochem. J. 370 (2003) 397–402.
[111] R.F. Burk, K.E. Hill, Selenoprotein P-expression, functions, and roles in mammals, Biochim. Biophys. Acta 1790 (2009) 1441–1447.
[112] M.B. Krol, J. Gromadzinska, W. Wasowicz, SeP, ApoER2 and megalin as necessary factors to maintain Se homeostasis in mammals, J. Trace Elem. Med. Biol. 26 (2012) 262–266.
[113] R.F. Burk, K.E. Hill, G.E. Olson, E.J. Weeber, A.K. Motley, V.P. Winfrey, L.M. Austin, Deletion of apolipoprotein E receptor-2 in mice lowers brain selenium and causes severe neurological dysfunction and death when a low-selenium diet is fed, J. Neurosci. 27 (2007) 6207–6211.
[114] J. Chiu-Ugalde, F. Theilig, T. Behrends, J. Drebes, C. Sieland, P. Subbarayal, J. Köhrle, A. Hammes, L. Schomburg, U. Schweizer, Mutation of megalin leads to urinary loss of selenoprotein P and selenium deficiency in serum, liver, kidneys and brain, Biochem. J. 431 (2010) 103–111.
[115] G.E. Olson, V.P. Winfrey, K.E. Hill, R.F. Burk, Megalin mediates selenoprotein P uptake by kidney proximal tubule epithelial cells, J. Biol. Chem. 283 (2008) 6854–6860.
[116] D. Behne, H. Hilmert, S. Scheid, H. Gessner, W. Elger, Evidence for specific selenium target tissues and new biologically important selenoproteins, Biochim. Biophys. Acta 966 (1988) 12–21.
[117] M. Kühbacher, J. Bartel, B. Hoppe, D. Alber, G. Bukalis, A.U. Bräuer, D. Behne, A. Kyriakopoulos, The brain selenoproteome: priorities in the hierarchy and different levels of selenium homeostasis in the brain of selenium-deficient rats, J. Neurochem. 110 (2009) 133–142.
[118] S.C. Schriever, K.M. Barnes, J.K. Evenson, A.M. Raines, R.A. Sunde, Selenium requirements are higher for glutathione peroxidase-1 mRNA than gpx1 activity in rat testis, Exp. Biol. Med. 234 (2009) 513–521.
[119] N. Pietschmann, E. Rijntjes, A. Hoeg, L. Schomburg, On the importance of selenium for bone physiology, Bone 51 (2012) S15.
[120] A. Nakayama, K.E. Hill, L.M. Austin, A.K. Motley, R.F. Burk, All regions of mouse brain are dependent on selenoprotein P for maintenance of selenium, J. Nutr. 137 (2007) 690–693.
[121] A. Hög, K. Renko, P. Seemann, U. Kornak, L. Schomburg, Reduced selenoprotein P expression affects bone formation, Endocr. Abstr. 20 (2009) OC6 (6).
[122] M.R. Bösl, K. Takaku, M. Oshima, S. Nishimura, M.M. Taketo, Early embryonic lethality caused by targeted disruption of the mouse selenocysteine tRNA gene (Trsp), Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 5531–5534.
[123] E. Kumaraswamy, B.A. Carlson, F. Morgan, K. Miyoshi, G.W. Robinson, D. Su, S. Wang, E. Southon, L. Tessarollo, B.J. Lee, V.N. Gladyshev, L. Hennighausen, D.L. Hatfield, Selective removal of the selenocysteine tRNA [Ser]Sec gene (Trsp) in mouse mammary epithelium, Mol. Cell. Biol. 23 (2003) 1477–1488.
[124] C.M. Downey, C.R. Horton, B.A. Carlson, T.E. Parsons, D.L. Hatfield, B. Hallgrímsson, F.R. Jirik, Osteo-chondroprogenitor-specific deletion of the selenocysteine tRNA gene, Trsp, leads to chondronecrosis and abnormal skeletal development: a putative model for Kashin–Beck disease, PLoS Genet. 5 (2009) e1000616.
[125] A. Wojcicka, J.H. Bassett, G.R. Williams, Mechanisms of action of thyroid hormones in the skeleton, Biochim. Biophys. Acta 1830 (2013) 3979–3986.
[126] J. Köhrle, F. Jakob, B. Contempré, J.E. Dumont, Selenium, the thyroid, and the endocrine system, Endocr. Rev. 26 (2006) 944–984.
[127] A.M. Dumitrescu, X.H. Liao, M.S. Abdullah, J. Lado-Abeal, F.A. Majed, L.C. Moeller, G. Boran, L. Schomburg, R.E. Weiss, S. Refetoff, Mutations in SECISBP2 result in abnormal thyroid hormone metabolism, Nat. Genet. 37 (2005) 1247–1252.
[128] M.F. Azevedo, G.B. Barra, L.A. Naves, L.F. Ribeiro Velasco, P. Godoy Garcia Castro, L.C. de Castro, A.A. Amato, A. Miniard, D. Driscoll, L. Schomburg, F. de Assis Rocha Neves, Selenoprotein-related disease in a young girl caused by nonsense mutations in the SBP2 gene, J. Clin. Endocrinol. Metab. 95 (2010) 4066–4071.
[129] C. Di Cosmo, N. McLellan, X.H. Liao, K.K. Khanna, R.E. Weiss, L. Papp, S. Refetoff, Clinical and molecular characterization of a novel selenocysteine insertion sequence-binding protein 2 (SBP2) gene mutation (R128X), J. Clin. Endocrinol. Metab. 94 (2009) 4003–4009.
[130] L. Schomburg, A.M. Dumitrescu, X.H. Liao, B. Bin-Abbas, J. Hoeflich, J. Köhrle, S. Refetoff, Selenium supplementation fails to correct the selenoprotein synthesis defect in subjects with SBP2 gene mutations, Thyroid 19 (2009) 277–281.
[131] T. Hamajima, Y. Mushimoto, H. Kobayashi, Y. Saito, K. Onigata, Novel compound heterozygous mutations in the SBP2 gene: characteristic clinical manifestations and the implications of GH and triiodothyronine in longitudinal bone growth and maturation, Eur. J. Endocrinol. 166 (2012) 757–764.
[132] J.J. Cao, B.R. Gregoire, H. Zeng, Selenium deficiency decreases antioxidative capacity and is detrimental to bone microarchitecture in mice, J. Nutr. 142 (2012) 1526–1531.
[133] R. Moreno-Reyes, D. Egrise, J. Nève, J.L. Pasteels, A. Schoutens, Selenium deficiency-induced growth retardation is associated with an impaired bone metabolism and osteopenia, J. Bone Miner. Res. 16 (2001) 1556–1563.
[134] F. Mathieu, F. Begaux, Z.Y. Lan, C. Suetens, M. Hinsenkamp, Clinical manifestations of Kashin–Beck disease in Nyemo Valley, Tibet, Int. Orthop. 21 (1997) 151–156.
[135] F. Mathieu, F. Begaux, C. Suetens, V. De Maertelaer, M. Hinsenkamp, Anthropometry and clinical features of Kashin–Beck disease in central Tibet, Int. Orthop. 25 (2001) 138–141.
[136] M. Hinsenkamp, F. Ryppens, F. Begaux, F. Mathieu, V. De Maertelaer, M. Lepeire, E. Haubruge, C. Chasseur, B. Stallenberg, The anatomical distribution of radiological abnormalities in Kashin–Beck disease in Tibet, Int. Orthop. 25 (2001) 142–146.
[137] G. Xiong, Diagnostic, clinical and radiological characteristics of Kashin–Beck disease in Shaanxi Province, PR China, Int. Orthop. 25 (2001) 147–150.
[138] Y. Jirong, P. Huiyun, Y. Zhongzhe, D. Birong, L. Weimin, Y. Ming, S. Yi, Sodium selenite for treatment of Kashin–Beck disease in children: a systematic review of randomised controlled trials, Osteoarthr. Cartil. 20 (2012) 605–613.
[139] R. Moreno-Reyes, C. Suetens, F. Mathieu, F. Begaux, D. Zhu, M.T. Rivera, M. Boelaert, J. Nève, N. Perlmutter, J. Vanderpas, Kashin–Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status, N. Engl. J. Med. 339 (1998) 1112–1120.
[140] R. Moreno-Reyes, F. Mathieu, M. Boelaert, F. Begaux, C. Suetens, M.T. Rivera, J. Nève, N. Perlmutter, J. Vanderpas, Selenium and iodine supplementation of rural Tibetan children affected by Kashin–Beck osteoarthropathy, Am. J. Clin. Nutr. 78 (2003) 137–144.
[141] A.J. Duffield, C.D. Thomson, K.E. Hill, S. Williams, An estimation of selenium requirements for New Zealanders, Am. J. Clin. Nutr. 70 (1999) 896–903.
[142] Y. Xia, K.E. Hill, D.W. Byrne, J. Xu, R.F. Burk, Effectiveness of selenium supplements in a low-selenium area of China, Am. J. Clin. Nutr. 81 (2005) 829–834.
[143] M.P. Rayman, The importance of selenium to human health, Lancet 356 (2000) 233–241.
[144] J. Nève, Human selenium supplementation as assessed by changes in blood selenium concentration and glutathione peroxidase activity, J. Trace Elem. Med. Biol. 9 (1995) 65–73.
[145] P. Kang, Y. Yao, J. Yang, B. Shen, Z. Zhou, F. Pei, An animal model of Kashin–Beck disease induced by a low-nutrition diet and exposure to T-2 toxin, Osteoarthr. Cartil. 21 (2013) 1108–1115.
[146] Y.F. Yao, F.X. Pei, X.B. Li, J. Yang, B. Shen, Z.K. Zhou, L. Li, P.D. Kang, Preventive effects of supplemental selenium and selenium plus iodine on bone and cartilage development in rats fed with diet from Kashin–Beck disease endemic area, Biol. Trace Elem. Res. 146 (2012) 199–206.
[147] Y. Yao, F. Pei, P. Kang, Selenium, iodine, and the relation with Kashin–Beck disease, Nutrition 27 (2011) 1095–1100.
[148] L.G. Raisz, Pathogenesis of osteoporosis: concepts, conflicts, and prospects, J. Clin. Invest. 115 (2005) 3318–3325.
[149] J. Lu, A. Holmgren, The thioredoxin antioxidant system, Free Radic. Biol. Med. 66 (2014) 75–87.
[150] S.X. Tan, D. Greetham, S. Raeth, C.M. Grant, I.W. Dawes, G.G. Perrone, The thioredoxin–thioredoxin reductase system can function in vivo as an alternative system to reduce oxidized glutathione in *Saccharomyces cerevisiae*, J. Biol. Chem. 285 (2010) 6118–6126.
[151] S.M. Kanzok, A. Fechner, H. Bauer, J.K. Ulschmid, H.M. Müller, J. Botella-Munoz, S. Schneuwly, R. Schirmer, K. Becker, Substitution of the thioredoxin system for glutathione reductase in *Drosophila melanogaster*, Science 291 (2001) 643–646.

[152] Y. Wang, H. Lu, D. Wang, S. Li, K. Sun, X. Wan, E.W. Taylor, J. Zhang, Inhibition of glutathione synthesis eliminates the adaptive response of ascitic hepatoma 22 cells to nedaplatin that targets thioredoxin reductase, Toxicol. Appl. Pharmacol. 265 (2012) 342–350.
[153] J. Zhang, H. Lu, Ifosfamide induces acute renal failure via inhibition of the thioredoxin reductase activity, Free Radic. Biol. Med. 43 (2007) 1574–1583.
[154] M.A. Fath, I.M. Ahmad, C.J. Smith, J. Spence, D.R. Spitz, Enhancement of carboplatin-mediated lung cancer cell killing by simultaneous disruption of glutathione and thioredoxin metabolism, Clin. Cancer Res. 17 (2011) 6206–6217.
[155] X. Wang, J. Zhang, T. Xu, Cyclophosphamide-evoked heart failure involves pronounced co-suppression of cytoplasmic thioredoxin reductase activity and non-protein free thiol level, Eur. J. Heart Fail. 11 (2009) 154–162.
[156] J. Lu, E.H. Chew, A. Holmgren, Targeting thioredoxin reductase is a basis for cancer therapy by arsenic trioxide, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 12288–12293.
[157] J.M. Lean, J.T. Davies, K. Fuller, C.J. Jagger, B. Kirstein, G.A. Partington, Z.L. Urry, T.J. Chambers, A crucial role for thiol antioxidants in estrogen-deficiency bone loss, J. Clin. Invest. 112 (2003) 915–923.
[158] S. Muthusami, I. Ramachandran, B. Muthusamy, G. Vasudevan, V. Prabhu, V. Subramaniam, A. Jagadeesan, S. Narasimha, Ovariectomy induces oxidative stress and impairs bone antioxidant system in adult rats, Clin. Chim. Acta 360 (2005) 81–86.
[159] R. Ebert, F. Jakob, Selenium deficiency as a putative risk factor for osteoporosis, Int. Congr. Ser. 1297 (2007) 158–164.
[160] A. Hoeg, A. Gogakos, E. Murphy, S. Mueller, J. Köhrle, D.M. Reid, C.C. Glüer, D. Felsenberg, C. Roux, R. Eastell, L. Schomburg, G.R. Williams, Bone turnover and bone mineral density are independently related to selenium status in healthy euthyroid postmenopausal women, J. Clin. Endocrinol. Metab. 97 (2012) 4061–4070.
[161] M.R. Law, A.K. Hackshaw, A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect, BMJ 315 (1997) 841–846.
[162] J. Zhang, R.G. Munger, N.A. West, D.R. Cutler, H.J. Wengreen, C.D. Corcoran, Antioxidant intake and risk of osteoporotic hip fracture in Utah: an effect modified by smoking status, Am. J. Epidemiol. 163 (2006) 9–17.
[163] P.P. Tak, G.S. Firestein, NF-kappaB: a key role in inflammatory diseases, J. Clin. Invest. 107 (2001) 7–11.
[164] A.V. Miagkov, D.V. Kovalenko, C.E. Brown, J.R. Didsbury, J.P. Cogswell, S.A. Stimpson, A.S. Baldwin, S.S. Makarov, NF-kappaB activation provides the potential link between inflammation and hyperplasia in the arthritic joint, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 13859–13864.
[165] Z. Han, D.L. Boyle, A.M. Manning, G.S. Firestein, AP-1 and NF-kappaB regulation in rheumatoid arthritis and murine collagen-induced arthritis, Autoimmunity 28 (1998) 197–208.
[166] P.W. Tsao, T. Suzuki, R. Totsuka, T. Murata, T. Takagi, Y. Ohmachi, H. Fujimura, I. Takata, The effect of dexamethasone on the expression of activated NF-kappa B in adjuvant arthritis, Clin. Immunol. Immunopathol. 83 (1997) 173–178.
[167] D.M. Gerlag, L. Ransone, P.P. Tak, Z. Han, M. Palanki, M.S. Barbosa, D. Boyle, A.M. Manning, G.S. Firestein, The effect of a T cell-specific NF-kappa B inhibitor on in vitro cytokine production and collagen-induced arthritis, J. Immunol. 165 (2000) 1652–1658.
[168] T. Tomita, E. Takeuchi, N. Tomita, R. Morishita, M. Kaneko, K. Yamamoto, T. Nakase, H. Seki, K. Kato, Y. Kaneda, T. Ochi, Suppressed severity of collagen-induced arthritis by in vivo transfection of nuclear factor kappaB decoy oligodeoxynucleotides as a gene therapy, Arthritis Rheum. 42 (1999) 2532–2542.
[169] R. Seetharaman, A.L. Mora, G. Nabozny, M. Boothby, J. Chen, Essential role of T cell NF-kappa B activation in collagen-induced arthritis, J. Immunol. 163 (1999) 1577–1583.
[170] H. Vunta, F. Davis, U.D. Palempalli, D. Bhat, R.J. Arner, J.T. Thompson, D.G. Peterson, C.C. Reddy, K.S. Prabhu, The anti-inflammatory effects of selenium are mediated through 15-deoxy-Delta12,14-prostaglandin J2 in macrophages, J. Biol. Chem. 282 (2007) 17964–17973.
[171] U.H. Gandhi, N. Kaushal, K.C. Ravindra, S. Hegde, S.M. Nelson, V. Narayan, H. Vunta, R.F. Paulson, K.S. Prabhu, Selenoprotein-dependent up-regulation of hematopoietic prostaglandin D2 synthase in macrophages is mediated through the activation of peroxisome proliferator-activated receptor (PPAR) gamma, J. Biol. Chem. 286 (2011) 27471–27482.
[172] H. Ueno, H. Kajihara, H. Nakamura, J. Yodoi, K. Nakamuro, Contribution of thioredoxin reductase to T-cell mitogenesis and NF-kappaB DNA-binding promoted by selenite, Antioxid. Redox Signal. 9 (2007) 115–121.
[173] I.Y. Kim, T.C. Stadtman, Inhibition of NF-kappaB DNA binding and nitric oxide induction in human T cells and lung adenocarcinoma cells by selenite treatment, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 12904–12907.
[174] A.T. Vieira, K.D. Silveira, M.C. Arruda, C.T. Fagundes, J.L. Gonçalves, T.A. Silva, M.J. Neves, M.A. Menezes, J.R. Nicoli, M.M. Teixeira, F.S. Martins, Treatment with Selemax®, a selenium-enriched yeast, ameliorates experimental arthritis in rats and mice, Br. J. Nutr. 108 (2012) 1829–1838.
[175] Y. Sakr, V.P. Maia, C. Santos, J. Stracke, M. Zeidan, O. Bayer, K. Reinhart, Adjuvant selenium supplementation in the form of sodium selenite in postoperative critically ill patients with severe sepsis, Crit. Care 18 (2014) R68.
[176] L. Schomburg, Selenium in sepsis — substitution, supplementation or pro-oxidative bolus? Crit. Care 18 (2014) 444.
[177] M.M. Maurice, H. Nakamura, S. Gringhuis, T. Okamoto, S. Yoshida, F. Kullmann, S. Lechner, E.A. van der Voort, A. Leow, J. Versendaal, U. Muller-Ladner, J. Yodoi, P.P. Tak, F.C. Breedveld, C.L. Verweij, Expression of the thioredoxin–thioredoxin reductase system in the inflamed joints of patients with rheumatoid arthritis, Arthritis Rheum. 42 (1999) 2430–2439.
[178] S. Yoshida, T. Katoh, T. Tetsuka, K. Uno, N. Matsui, T. Okamoto, Involvement of thioredoxin in rheumatoid arthritis: its costimulatory roles in the TNF-alpha-induced production of IL-6 and IL-8 from cultured synovial fibroblasts, J. Immunol. 163 (1999) 351–358.
[179] Y. Kabuyama, T. Kitamura, J. Yamaki, M.K. Homma, S. Kikuchi, Y. Homma, Involvement of thioredoxin reductase 1 in the regulation of redox balance and viability of rheumatoid synovial cells, Biochem. Biophys. Res. Commun. 367 (2008) 491–496.
[180] H. Lemarechal, P. Anract, J.L. Beaudeux, D. Bonnefont-Rousselot, O.G. Ekindjian, D. Borderie, Impairment of thioredoxin reductase activity by oxidative stress in human rheumatoid synoviocytes, Free Radic. Res. 41 (2007) 688–698.
[181] W.F. Kean, I.R. Kean, Clinical pharmacology of gold, Inflammopharmacology 16 (2008) 112–125.
[182] A. Lipton, R. Uzzo, R.J. Amato, G.K. Ellis, B. Hakimian, G.D. Roodman, M.R. Smith, The science and practice of bone health in oncology: managing bone loss and metastasis in patients with solid tumors, J. Natl. Compr. Cancer Netw. 7 (2009) S1–S29.
[183] Y.C. Chen, D.M. Sosnoski, A.M. Mastro, Breast cancer metastasis to the bone: mechanisms of bone loss, Breast Cancer Res. 12 (2010) 215.
[184] Y.C. Chen, D.M. Sosnoski, U.H. Gandhi, L.J. Novinger, K.S. Prabhu, A.M. Mastro, Selenium modifies the osteoblast inflammatory stress response to bone metastatic breast cancer, Carcinogenesis 30 (2009) 1941–1948.
[185] T. Standal, M. Borset, A. Sundan, Role of osteopontin in adhesion, migration, cell survival and bone remodeling, Exp. Oncol. 26 (2006) 179–184.
[186] H. Ihara, D.T. Denhardt, K. Furuya, T. Yamashita, Y. Muguruma, K. Tsuji, K.A. Hruska, K. Higashio, S. Enomoto, A. Nifuji, S.R. Rittling, M. Noda, Parathyroid hormone-induced bone resorption does not occur in the absence of osteopontin, J. Biol. Chem. 276 (2001) 13065–13071.
[187] H. Yoshitake, S.R. Rittling, D.T. Denhardt, M. Noda, Osteopontin-deficient mice are resistant to ovariectomy-induced bone resorption, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 8156–8160.
[188] T. Ishii, S. Ohshima, T. Ishida, T. Mima, Y. Tabunoki, H. Kobayashi, M. Maeda, T. Uede, L. Liaw, N. Kinoshita, I. Kawase, Y. Saeki, Osteopontin as a positive regulator in the osteoclastogenesis of arthritis, Biochem. Biophys. Res. Commun. 316 (2004) 809–815.
[189] K.A. Furger, R.K. Menon, A.B. Tuck, V.H. Bramwell, A.F. Chambers, The functional and clinical roles of osteopontin in cancer and metastasis, Curr. Mol. Med. 1 (2001) 621–632.
[190] T.G. Hullinger, R.S. Taichman, D.A. Linseman, M.J. Somerman, Secretory products from PC-3 and MCF-7 tumor cell lines upregulate osteopontin in MC3T3-E1 cells, J. Cell. Biochem. 78 (2000) 607–616.
[191] H. Singhal, D.S. Bautista, K.S. Tonkin, F.P. O'Malley, A.B. Tuck, A.F. Chambers, J.F. Harris, Elevated plasma osteopontin in metastatic breast cancer associated with increased tumor burden and decreased survival, Clin. Cancer Res. 3 (1997) 605–611.
[192] Y.J. Chen, J.L. Shen, C.Y. Wu, Y.T. Chang, C.M. Chen, F.Y. Lee, Elevated plasma osteopontin level is associated with occurrence of psoriasis and is an unfavorable cardiovascular risk factor in patients with psoriasis, J. Am. Acad. Dermatol. 60 (2009) 225–230.
[193] A.B. Serwin, W. Wasowicz, J. Gromadzinska, B. Chodynicka, Selenium status in psoriasis and its relations to the duration and severity of the disease, Nutrition 19 (2003) 301–304.
[194] D. Kadry, L. Rashed, Plasma and tissue osteopontin in relation to plasma selenium in patients with psoriasis, J. Eur. Acad. Dermatol. Venereol. 26 (2012) 66–70.
[195] P.J. Marie, Transcription factors controlling osteoblastogenesis, Arch. Biochem. Biophys. 473 (2008) 98–105.
[196] H. Liu, Q. Lu, K. Huang, Selenium suppressed hydrogen peroxide-induced vascular smooth muscle cells calcification through inhibiting oxidative stress and ERK activation, J. Cell. Biochem. 111 (2010) 1556–1564.
[197] E. Unni, F.S. Kittrell, U. Singh, R. Sinha, Osteopontin is a potential target gene in mouse mammary cancer chemoprevention by Se-methylselenocysteine, Breast Cancer Res. 6 (2004) R586–R592.
[198] P.H. Anborgh, J.C. Mutrie, A.B. Tuck, A.F. Chambers, Role of the metastasis-promoting protein osteopontin in the tumour microenvironment, J. Cell. Mol. Med. 14 (2010) 2037–2044.
[199] N.I. Johnston, V.K. Gunasekharan, A. Ravindranath, C. O'Connell, P.G. Johnston, M.K. El-Tanani, Osteopontin as a target for cancer therapy, Front. Biosci. 13 (2008) 4361–4372.
[200] M.K. El-Tanani, Role of osteopontin in cellular signaling and metastatic phenotype, Front. Biosci. 13 (2008) 4276–4284.
[201] Y.C. Chen, K.S. Prabhu, A.M. Mastro, Is selenium a potential treatment for cancer metastasis? Nutrients 5 (2013) 1149–1168.
[202] Y.C. Chen, K.S. Prabhu, A. Das, A.M. Mastro, Dietary selenium supplementation modifies breast tumor growth and metastasis, Int. J. Cancer 133 (2013) 2054–2064.
[203] P. Hadji, M.S. Aapro, J.J. Body, N.J. Bundred, A. Brufsky, R.E. Coleman, M. Gnant, T. Guise, A. Lipton, Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment, Ann. Oncol. 22 (2011) 2546–2555.
[204] P. Hadji, J.J. Body, M.S. Aapro, A. Brufsky, R.E. Coleman, T. Guise, A. Lipton, M. Tubiana-Hulin, Practical guidance for the management of aromatase inhibitor-associated bone loss, Ann. Oncol. 19 (2008) 1407–1416.
[205] R. Rizzoli, J.J. Body, A. DeCensi, J.Y. Reginster, P. Piscitelli, M.L. Brandi, European Society for Clinical and Economical aspects of Osteoporosis and Osteoarthritis (ESCEO), Guidance for the prevention of bone loss and fractures in postmenopausal women treated with aromatase inhibitors for breast cancer: an ESCEO position paper, Osteoporos. Int. 23 (2012) 2567–2576.

[206] K.K. Vekariya, J. Kaur, K. Tikoo, Alleviating anastrozole induced bone toxicity by selenium nanoparticles in SD rats, Toxicol. Appl. Pharmacol. 268 (2013) 212–220.
[207] N. Metes-Kosik, I. Luptak, P.M. Dibello, D.E. Handy, S.S. Tang, H. Zhi, F. Qin, D.W. Jacobsen, J. Loscalzo, J. Joseph, Both selenium deficiency and modest selenium supplementation lead to myocardial fibrosis in mice via effects on redox-methylation balance, Mol. Nutr. Food Res. 56 (2012) 1812–1824.
[208] H. Steinbrenner, B. Speckmann, H. Sies, Toward understanding success and failures in the use of selenium for cancer prevention, Antioxid. Redox Signal. 19 (2013) 181–191.
[209] M.P. Rayman, Selenium and human health, Lancet 379 (2012) 1256–1268.