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Review

Selenium-related transcriptional regulation of gene expression

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Abstract: Selenium is a trace metal essential to human health, and its deficiency has been related to, for instance, cardiovascular and myodegenerative diseases, infertility and osteochondropathy Kashin-Beck disease. It is incorporated as selenocysteine to selenoproteins, which protect against reactive oxygen and nitrogen species. They also participate in the activation of thyroid hormone, and play a role in immune system functioning. The synthesis and incorporation of selenocysteine occurs via a special mechanism, which differs from the one used for standard amino acids. The codon for selenocysteine is the regular in-frame stop codon, which can be passed by specific complex machinery participating in translation elongation and termination. This includes the presence of selenocysteine insertion sequence (SECIS) in the 3'-untranslated part of the selenoprotein mRNAs. Selenium deficiency is known to control both selenoprotein and non-selenoprotein transcriptomes. Nonsense-mediated decay is involved in the regulation of selenoprotein mRNA levels, both other mechanisms are also possible.

Keywords: selenium; selenocysteine; selenoproteins; selenocysteine insertion sequence; nonsense-mediated decay

1. Introduction

Selenium is a trace metal and a vital nutrient component. It is bioavailable in organic form as selenomethionine and selenocysteine, and as inorganic selenate and selenite in supplemental forms. Recommended average daily intake for individuals over 14 years of age is 55 μg according to the Office of Dietary Supplements of the National Institutes of Health (Bethesda, MD, USA), while the need in younger children ranges between 15-40 μg/day. Globally, the dietary intake can often be below that recommendation [1], and there may be even one billion people affected by selenium deficiency, mainly due to low selenium content in the soil. Geographical variation in soil selenium content occurs globally, and especially in China soil shows highly variable contents [2]. Chinese endemic diseases, such as Keshan and Kashin-Beck diseases are mainly observed in geographical northeast to southwest belt with a very low content of water-soluble selenium [3]. Selenium deficiency is associated also with fibrosis of various organs, such as heart, liver, kidney, thyroid and pancreas, and cystic and oral submucous fibrosis [4].

In 1970's, Finland was among those countries, which had lowest selenium levels in the population. Since Finland also had high incidence of cardiovascular diseases, an association of these factors was hypothesized. A large-scale fortification of fertilizers with selenium increased selenium contents of bread and milk in Finland so that selenium levels in serum almost doubled in the population [5]. While selenium deficiency is related to many diseases, selenium is also toxic at higher concentrations, and can even interact with arsenic [6].

In this review, we briefly discuss the functions of selenoproteins, the events related to selenoprotein biosynthesis, and how selenium deficiency affects the gene regulation of

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selenoproteins, but also other genes. The role of long non-coding RNAs (lncRNAs) is also handled, while the focus of this review is on human and other mammalian observations.

2. Selenoprotein functions and selenoprotein-related disorders

Selenium is incorporated into proteins mainly as amino acid selenocysteine (Sec), the 21st amino acid [7]. There are 24 selenoproteins identified in rodents and 25 in human [8]. These include five glutathione peroxidases, three iodothyronine deiodinases, two thioredoxin reductases, thioredoxin-glutathione reductase 3, selenophosphate synthetase 2, methionine sulfoxide reductase B1, and selenoproteins F, H, I, K, M, N, O, P, S, T, V and W [9]. The best known selenoproteins are the glutathione peroxidases, the thioredoxin reductases, the iodothyronine deiodinases and selenoprotein P.

Selenoprotein biosynthesis is essential for life, since deletion of the murine gene encoding selenocysteine tRNA, which inserts selenocysteine amino acid to growing polypeptide during translation, led to early embryonic lethality [10]. Functions of many of the selenoproteins have been identied so far, although there are still those with unknown function [11]. Almost all of them are oxidoreductases, and they have been localized to plasma membrane, endoplasmic reticulum, cytosol, mitochondria, and nucleus, and even two secreted extracellular selenoproteins are present [11]. They also have diverse patterns of tissue distribution, which can vary from ubiquitous to very tissue-specific locations [12]. The selenoproteins involve antioxidant and redox reactions by detoxification of peroxides, regeneration of reduced thioredoxin and reduction of oxidized methionine residues, and iodothyronine deiodinases regulate the activity of thyroid hormone [12]. Some selenoproteins are also involved in calcium mobilization, selenium transport and endoplasmic reticulum stress [12].

Universal genetic code has 3 codons reserved for transcription termination. Of those, UGA codon signals also for the incorporation of Sec into the selenoproteins [13]. A Sec insertion sequence (SECIS), which is a specific stem-loop structure in the 3'-untranslated regions (UTRs) of the messenger RNAs (mRNAs) in eukaryotes, makes cotranslational incorporation of Sec into nascent polypeptides possible [14]. Mammalian selenoproteins usually contain single Sec residue located in the enzymes'active site, with the exception of selenoprotein P, which has multiple ones [15]. The presence of Sec in the active site of selenoproteins is important for its activity, and misinterpretation of UGA codon can lead to significant loss of function of the selenoprotein. Still, many selenoproteins have functional orthologs, which have cysteine occupying the position of Sec [16], although usually having a poor activity in comparison to Sec-containing selenoprotein.

Mutations and inborn errors in genes involved in selenoprotein biosynthesis have been identified [17]. The first selenoprotein-related mutations were observed in selenoprotein N [18], and it has been noticed that mutations in selenoprotein N lead to a spectrum of myopathies. Other disorders include neurologic phenotypes due to, for instance, selenium deficiency in the brain caused impaired selenium transport in selenoprotein P deficient mice [19,20]. Mutations in glutathione peroxidase 4 cause Sedaghatian-type spondylometaphyseal chondrodysplasia [21], and those in thioredoxin system may affect heart and adrenals [22,23]. There are no known mutations of iodothyronine deiodinases in human, but in mouse deletion of iodothyronine deiodinase 2 impaired bone stability [24]. Mutations in SECIS-binding protein 2 gene affect thyroid hormone regulation [25], but can have variable other features as well. The first identified human mutation in selenocysteine transfer RNA ($tRNA^{[Ser]\ Sec}$) manifested similar phenotype as mutations in SECIS-binding protein 2 gene [26]. In mouse, a deletion of gene encoding the $tRNA^{[Ser]\ Sec}$ in osteochondroprogenitor yields a phenotype similar to Kashin-Beck disease [27], although the phenotype is clearly stronger than the one observed in human Kashin-Beck disease [28].

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3. Biosynthesis of selenocysteine and selenoproteins

There are two principal elements in the biosynthesis of selenoproteins and recoding of the UGA stop codon [29]. These are the involvement of 1) $tRNA^{[Ser]\ Sec}$, which has the anticodon to the UGA codon, and 2) SECIS in the 3'-end UTR. $tRNA^{[Ser]\ Sec}$, which was first described in 1970 [30,31], is a unique tRNA in having the possibility to control a whole class of proteins, namely selenoproteins.

The aminoacylation of $tRNA^{[Ser]\ Sec}$ remarkably differs from the other tRNAs, since it requires the action of four different enzymes instead of only one needed for the other ones [29]. In eukaryotes, the synthesis of Sec is started so that serine aminoacyl tRNA synthetase charges $tRNA^{[Ser]\ Sec}$ with serine amino acid. In the next step, $tRNA^{[Ser]\ Sec}$ serine is phosphorylated by a specific phosphoseryl tRNA kinase and, finally, the phosphate of O-phosphoserine of the $tRNA^{[Ser]\ Sec}$ is substituted by selenium atom donated by selenophosphate in a reaction catalyzed by selenocysteine synthase [29]. Selenophosphate synthetases 1 and 2 activate the selenium in selenophosphate [32,33].

Every selenoprotein mRNA contains a stem-loop-stem-loop structure in the 3'-end of their mRNA, which is approximately 200 nucleotides long sequence. They are essential for the recoding of the UGA codons during selenoprotein translation. It has been noticed that SECIS motif is in fact important for the modulation of the efficiency of Sec insertion, so that several thousand-fold differences can be observed between the strongest and weakest SECIS elements [34]. The minimum distance of SECIS motif from the UGA codon is evaluated to be 51-111 nucleotides [35].

There are many proteins involved in recoding of Sec. The best characterized of those is SECIS-binding protein 2 (SBP2) [36], which is found in all eukaryotes expressing selenoproteins. It is one of the limiting factors for Sec insertion [37], and its silencing caused a selective down-regulation of selenoprotein expression in mammalian cells [38]. It has been shown that SBP2 binding affinity also has a major importance for differential selenoprotein mRNA translation and sensitivity to so-called nonsense-mediated decay (NMD) [39]. The cells use a complex NMD pathway to destroy mRNAs with premature stop codon to prevent their translation, which would lead to synthesis of incorrect proteins [40]. Translation initiation factor 4A3 (eIF4A3) is a SECIS-binding protein, which takes part in selective translational control of a subset of selenoproteins [41]. Its binding to a subset of SECIS elements physically limits the binding of SBP2 there, thus, preventing Sec insertion [41], and leads to premature stop of transcription. It has been shown that approximately half of the selenoprotein transcriptome has SECIS element susceptible for NMD, which leads to remarkable changes under selenium deficiency [42].

Ribosomal protein L30 is SECIS-binding protein as a component of the large unit of eukaryotic ribosome, and apparently can recruit SBP2 to the Sec recoding machinery [43], but its exact function in Sec insertion needs further investigations. A multifunctional protein, nucleolin, is another SECIS-binding protein, which in Sec translation complex likely functions as a link to the ribosome [44].

4. Regulation of selenoprotein transcriptome by selenium

Selenium intake has been observed to affect significantly the selenoproteome. In selenium deficiency, the production of certain obviously essential selenoproteins is prioritized over the others [45,46]. In one-day old layer chicken liver, a prolonged deficiency of selenium of the diet continued for up to 65 days decreased 19 selenoprotein mRNA expressions of 21 investigated ones [47]. However, the sensitivity of various selenoprotein gene expression to decrease was differential [47]. In general, interpretations of the results accumulated from published studies are somewhat complicated, since the tissue distribution of the specific selenoproteins and their various intra- and extracellular locations is variable [11,48].

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4.1. Glutathione peroxidases

Five of the glutathione peroxidases in human are selenoproteins [49]. Glutathione peroxidases are catalysts for reduction of H_2O_2 or organic hydroxyperoxides to water or corresponding alcohols, most often using glutathione as a reductant. Their dysregulation has been noticed to associate with diabetes, cancer, inflammation, and obesity [49].

Ubiquitously present glutathione peroxidase 1 was the first identified selenoprotein, which was then found to protect hemoglobin from oxidative breakdown [50]. Its gene expression and enzyme activity was almost totally lost in liver and heart under depletion of selenium in diet of rats, while glutathione peroxidase 4 (also known as phospholipid hydroperoxide glutathione reductase) gene expression was practically unchanged despite the 75% and 60% decrease of enzymatic activity [48].

In rats, glutathione peroxidase 2 was observed to be expressed only in the epithelium of gastrointestinal tract, therefore, it is also called gastrointestinal glutathione peroxidase [51], although expression in liver was also reported for human liver [52]. Selenium deficiency even appeared to increase the gene expression of glutathione peroxidase 2, while glutathione peroxidase 1 levels dropped and glutathione peroxidase 4 levels remained unchanged [53].

Glutathione peroxidase 3 is an abundant plasma protein, which is mostly secreted kidney proximal tubules [54]. Studies with double knock-out mice for glutathione peroxidase 3 and selenoprotein P showed that together these two proteins account for most part (>97%) of all plasma selenium in mice [55].

Besides H_2O_2, glutathione peroxidase 4 can reduce also hydroperoxides present in phospholipids and cholesterol [49]. It is present in three different isoform, which are cytosolic, mitochondrial and sperm nuclear ones [56]. They have been shown to be relatively resistant to selenium deficiency [38,48], and are considered to be among the essential selenoproteins [57].

4.2. Thioredoxin reductases

Humans and higher eukaryotes have three thioredoxin reductases, which are cytosolic, mitochondrial and testis specific ones [58], which all contain an in-frame UGA codon to encode Sec residue. Although mutation of Sec to Cys leads to major decrease in their catalytic activity, Sec is not catalytically essential to reduce thioredoxin due to orthologs, which can perform identical reactions with approximately same efficiencies [59]. Thioredoxin reductase 1 has been shown to be different from thioredoxin reductase 3 by containing a C-terminal structure, which restricts the motion of the C-terminal tail containing Gly-Cys-Sec-Gly tetrapeptide so that only that C-terminal redox center can participate with Se-dependent reduction by the N-terminal redox center, while thioredoxin reductase 3 does not have that same structure [60]. Therefore, thioredoxin reductase 3 has a greater access of the substrate and an alternative mechanistic pathway [60].

Selenium deficiency was shown to decrease both thioredoxin reductases 1 and 2 in rat heart, as well as glutathione reductases 1 and 4, which is known to impair the recovery from ischemia-reperfusion, while selenium supplementation significantly increased their expression levels [61]. Although glutathione peroxidases and thioredoxin reductases have been shown to be similarly modulated by selenium availability in cardiac tissue [61], and to cooperate in the protection against free-radical-mediated cell death [62], they were oppositely regulated by selenium in response to replicative senescence in human embryonic fibroblasts [63].

Thioredoxin reductase 1 is overexpressed in many malignant cells and, thus, it has been considered as a target for anticancer approaches [64]. The transcriptional regulation of human thioredoxin reductase is very complex [65]. It has at least 21 different transcripts, which encode five isoforms differing in the alternative N-terminal domains [66]. It has been been observed that selenium overdose can have selective cytotoxic effects on tumor cells [67].

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4.3. Iodothyronine deiodinases

Type 1 iodothyronine deiodinase produces biologically active 3,5,3'-triiodothyronine (T3) from 3,5,3',5'-tetraiodothyronine (T4, or thyroxin) for the plasma, while type II enzyme provides the local conversion. Type 3 enzyme finally converts T3 to inactive T2. All three deiodinases are expressed in a number of fetal and adult tissues [68]. The finding that selenium deficiency inhibits the activity of type I and II iodothyronine deiodinases led to the proposal that they are seleno-enzymes or selenium-containing cofactors [69], and type I iodothyronine deiodinase was soon identified as a selenoenzyme [70]. However, the gene expressions of type I iodothyronine deiodinase and selenoprotein P were more resistant to selenium deficiency-related decline than glutathione reductase [71]. In chicken, type I deiodinase was the most sensitive to prolonged selenium deficiency, while type III enzyme did not change significantly even after 65 days deprivation [47]. Thyroid is much more resistant to dietary deficiency than, for instance, liver, indicating the dependency on the organ how selenium deprivation affects the gene expression of selenoproteins [72]. Although the thyroid function of iodothyronine deiodinases is understandably important for thyroidal conversion of T4 to T3, type I iodothyronine deiodinase transcripts could be found even at higher levels than thyroid in ovine skeletal muscle, kidney and heart, while type II iodothyronine deiodinase transcription levels were the highest in ovine thyroid [73].

4.4. Other selenoproteins

A number of other selenoproteins gene expressions are regulated by selenium availability. In chicken, selenoprotein I was the only one, which did not show significant decrease at mRNA levels even after 65 days of selenium deficiency, while all the other investigated ones had decreased levels already after 15 days treatment [47].

Selenoprotein P is unique among the selenoprotein containing several Sec residues, in human 10 Secs [74]. It is an extracellular protein, which contains 40-50% of the total selenium in plasma. Liver takes up selenium and incorporates it into selenoprotein P, which is then secreted into plasma for transport to other tissues [75]. Deletion of selenoprotein P gene affected low selenium diet-related depression of selenium content most severely in the brain and the testis, while heart was not affected [76]. Due to its selenium transport characteristics, selenoprotein P has a special role also in the regulation of other selenoproteins.

Selenophosphate-synthetase 2 is an enzyme, which participates the biosynthesis of selenoproteins by providing selenophosphate needed in the biosynthesis of Sec. Thus, it can regulate its own production besides with the production of other selenoproteins [77]. In selenoprotein P depleted mice, all the other selenoproteins were down-regulated in the brain and testis, in contrast to elevated level of selenophosphate-synthetase 2 [78], which obviously can provide compensatory mechanism during lo selenium conditions.

Recent selenoproteome transcriptome study showed that selenium deficiency in ATDC chondrocyte cell line dropped most dramatically the expression levels of glutathione peroxidase 1 and selenoproteins H, I and W, while selenophosphate synthetase 2 and selenoproteins O, R and S were in fact upregulated [79]. Glutathione peroxidase 1, thioredoxin reductase 1 and selenoproteins H, P, R and W were the most efficient to increase their gene expression after repletion of selenium to selenium-deficient medium [79]. Similar results were obtained with another chondrocyte cell line C28/I2 [79]. A microarray analyses showed that nine selenoproteins were significantly down-regulated in selenium-deficient liver, while in mice with marginal selenium status none of these transcripts remained decreased relative to levels in selenium adequate mice [80]. This was concluded to mean that selenium-related regulation of selenoprotein gene expression is mediated by one underlying mechanism [46].

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5. Regulation of non-selenoprotein transcriptome by selenium

Selenium deficiency regulates also the expression of genes other than those encoding for the selenoproteins. Although limited in number, the recent large-scale transcriptome and proteome analyses have given new insights into the general level effects of selenium deprivation.

Microarray data of more than 30,000 transcripts from livers of rats fed with 0-5 μg selenium/g diet revealed that selenium deficiency down-regulated four selenoprotein genes (glutathione peroxidase 1, thioredoxin reductase 3, and selenoproteins H and T), while in mouse also thioredoxin reductase 2 and selenoproteins K and W, muscle 1 were down-regulated in liver, and selenoprotein W, muscle 1 in kidney [81]. Only two transcripts (UDP-glucuronosyltransferase 2 family, polypeptide B7 and glutathione S-transferase Yc2 subunit) were up-regulated in rat liver [81], whereas carbonyl reductase 3 and heat shock protein 1 in mouse liver and glutathione 5-transferase, alpha 3 in mouse kidney were also induced [81]. Real-time polymerase chain reaction analyses of rat liver indicated also ATP-binding cassette, subfamily C (CFTR/MRP), member 3 and NADPH dehydrogenase, quinone 1 to be upregulated genes [81], the targets of nuclear factor, erythroid-2 like factor 2 (Nrf2) [81]. The Nrf2 is a master regulator of the cellular antioxidant response [82], and plays a critical role in cancer prevention, thus, relating to the anti-cancer properties of selenium.

In the range of 0.08 to 0.8 μg selenium/g diet there were no remarkable differences in the gene expressions, while 2 μg selenium/g diet upregulated the following transcripts: regulator of G-protein signaling 4, coiled-coil domain containing 80, RGD1560666, 3-oxoacid CoA transferase 1, and EST UI-R-BS1-ayq-f-06-0-UI.s1. The only down-regulated one was cold-inducible RNA binding protein in comparison to selenium adequate diet [81].

The biggest number of changed gene expressions was achieved by selenium levels considered already toxic. There were 1193 transcripts, which were significantly changed [81]. Since the rats fed with 5 μg selenium/g diet had retarded growth and signs of liver damage markers, the transcripts were filtered against changed transcripts in calory restricted rats [83] and those overlapping Affymetrix's Rat ToxFX 1.o array, and duplicate transcripts were also removed. This reduced the number of transcripts regarded to be most likely selenium-specific to 667 unique ones [81]. Gene ontology analyses revealed a number of biological processes related to cellular movement and morphogenesis, extracellular matrix and cytoskeleton organization, and development and angiogenesis affected by toxic level of selenium [81].

6. Selenium regulation of microRNAs and long non-coding RNAs

Besides mRNAs the cells express groups of non-protein-coding transcripts, which can regulate a wide array of protein coding genes. MicroRNAs (miRNAs) and lncRNAs are two major families of them. In intestinal cell line, selenium deficiency changed the expression of 50 genes and twelve miRNAs. Pathways related to, for instance, arachidonic acid metabolism, glutathione metabolism, oxidative stress, and mitochondrial respiration were found to be selenium-sensitive. Besides, thirteen transcripts were predicted to be targets for the selenium-sensitive miRNAs, three of which were recognized by miR-185. More importantly, silencing of miR-185 increased glutathione peroxidase 2 and selenophosphate synthetase 2. [84]. In a recent study, several miRNAs were predicted as putative regulators of various glutathione peroxidases [85].

In hepatocarcinoma cell line, it was noticed that miRNA-544a interacted with selenoprotein K, suppressing its expression, and selenium treatment was able to modulate miR-544a expression [86]. On the other hand, selenium increased the expression level of miR-125a, and overexpression of miR-125a could inhibit cadmium-induced apoptosis in [87]. In selenium-deficient rats, the cardiac dysfunction was mainly associated with five up-regulated miRNAs (miR-374, miR-16, miR-199a-5p, miR-195 and miR-30e) and three down-regulated ones (miR-3571, miR-675 and miR-450a) [88]. In Caco-2 human adenocarcinoma cells, ten selenium-sensitive miRNAs were identified, which are involved in the regulation of 3588 mRNAs. Pathway analysis indicated them to participate in pathways such as the cell cycle, the cellular response to stress, the canonical Wnt/ -catenin, p53 and mitogen-activated kinase signaling pathways [89].

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Only two publications, which have investigated the regulation of lncRNAs by selenium, could be found. The first one investigated lncRNAs in vascular exudative diathesis of chicken, induced by selenium deficiency. A total of 635 differentially expressed lncRNAs out of 15412 detected ones were identified, gene ontology analysis showing importance of oxidative reduction in particular. The study could verify that 19 target mRNAs of 23 lncRNAs were related to oxidative reduction process. [90]

The other study investigated the role of lncRNAs in selenium deficiency induced muscle injury in chicken. The study identified 38 lncRNAs and 687 mRNAs, which were affected by selenium deficiency. Pathway analyses revealed dysregulated pathways associated with phagosomes, cardiac muscle contraction, and peroxisome proliferator-activated receptor (PPAR) in selenium-deficient group. In particular the study showed a relationship between lncRNA ALDBGAL0000005049 and stearoyl-CoA desaturase in PPAR pathway. The down-regulation of that lncRNA led to inflammation by regulating the stearoyl-CoA desaturase gene expression. [91]

Research on non-protein-coding RNAs is still limited in numbers, and future investigations will certainly shed new light on how they are involved in selenium-related gene expresssions. The present studies already show that they are potential regulators of the cellular responses and gene expressions.

7. Selenium-related gene expressions in some pathological conditions

Selenium has been associated with a number of pathological conditions. Although the mechanism how selenium is related to the pathogenesis is not always very precisely known, new research results may give new ideas to understand the selenium-related diseases.

Keshan disease is an endemic cardiomyopathy related to selenium deficiency leading to a high mortality rate. To understand better the molecular mechanism of Keshan disease pathogenesis, a proteomic screening of peripheral blood sera was performed with mass spectrometry to identify differentially expressed selenium- and zinc-related proteins and their pathway and networks associated with Keshan disease [92]. In total of nineteen selenium- and three zinc-associated proteins were identified among 105 differentially expressed proteins [92]. Pathway analysis revealed 52 pathways, of which hypoxia-inducible factor-1α and apoptosis pathways are likely to play a role in selenium-associated functions [92]. A study combining custom-made microarray (containing 78 probes previously differentially expressed genes in Keshan disease) analyses performed for peripheral blood mononuclear cell RNA samples obtained from 100 Keshan disease patients and 100 normal controls, and mass spectrometric proteomic analyses of peripheral blood sera indicated that there are numerous functional categories associated with differentially expressed genes and proteins [93]. The limitations of these studies are the fact that the selenium status of the individuals was not known.

Selenium deficiency has also been associated to Kashin-Beck disease, an endemic osteochondropathy. The differentially expressed genes in the transcriptome analyses comparing cartilage samples from Kashin-Beck disease versus normal control [94] or versus osteoarthritis [95] were other than selenoproteins. Pathways related to reactive oxygen species and vascular endothelial growth factor were significantly elevated in osteoarthritis compared with Kashin-Beck disease, while expressions of collagen- and nitric oxide-related pathway elevated in Kashin-Beck disease [96]. Analysis of mitochondria-related genes identified nine more up-regulated genes in Kashin-Beck disease versus normal control involved in three canonical pathways of oxidative phosphorylation, apoptosis signaling and pyruvate metabolism [97]. Expression profiles in cultured chondrocytes revealed 232 up- and 427 down-regulated mRNAs and 316 up- and 631 down-regulated lncRNAs [98]. A lncRNA-mRNA correlation analysis yielded 509 coding-noncoding gene co-expression networks, and eleven lncRNAs were predicted to have *cis*-regulated target genes, and co-expressed mRNAs and lncRNAs formed large network associated with the biological events of extracellular matrix [98].

The problem with investigations on Kashin-Beck disease is that it often develops already at early childhood. Due to the poor regeneration of articular cartilage, collection of biopsies from

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juvenile cartilage is not normally justified. The diet in Kashin-Beck endemic areas has also changed due to selenium supplementation [99]. Thus, the samples collected at later life most likely do not reflect the physiological or selenium status present at the onset of the disease. Nevertheless, a recent study, which estimated the nutrient intakes of children, showed that daily intakes of multiple nutrient, not only selenium, were lower in selenium-supplemented Kashin-Beck area in comparison to non-selenium-supplemented areas [100]. There were 116 nutrients-related differentially expressed genes in periopheral blood of Kashin-Beck disease children (51 up- and 65 down-regulated ones), and 10 significant pathways were also recognized using KEGG and REACTOME network databases [100]. Overlapping genes with various functions associated with different nutrients, as well [100].

8. Conclusions

The transcription and translation of selenoproteins require a specific and complex cellular machinery. Selenium status can define the expression levels of selenoprotein mRNA transcripts, although there is some degree of organ- and species-dependent variation. Also expressions of non-selenoprotein genes are affected by selenium status, but more research is warranted to gain deeper understanding of the interacting pathways and functions.

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Abbreviations

eIF4A3	Translation initiation factor 4A3
lncRNA	Long non-coding RNA
miRNA	Micro RNA
mRNA	Messenger RNA
NMD	Nonsense-mediated decay
Nrf2	Nuclear factor, erythroid-2 like factor 2
PPAR	Peroxisome proliferator-activated receptor
SBP2	SECIS-binding protein 2
Sec	Selenocysteine
SECIS	Selenocysteine insertion sequence
SNP	Single-nucleotide polymorphism
tRNA	Transfer RNA
$tRNA^{[Ser]\,Sec}$	Selenocysteine transfer RNA
UTR	3′-untranslated region of messenger RNA
T3	3,5,3′-Triiodothyronine
T4	3,5,3,5′′-Tetraiodothyronine

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