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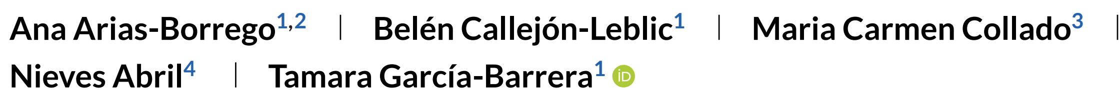
Proteomics
Proteomics and Systems Biology

REVIEW

Omics insights into the responses to dietary selenium



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Abstract

Selenium is a well-known health-relevant element related with cancer chemoprevention, neuroprotective roles, beneficial in diabetes, and in several infectious diseases, among others. It is naturally present in some foods, but deficiency in people led to the production of nutraceuticals, supplements, and functional food enriched in this element. There is a U-shaped link between selenium levels and health and a narrow range between toxic and essential levels, and thus, supplementation should be performed carefully. Omics methodologies have become valuable approaches to delve into the responses of dietary selenium in mammals that allowed a deeper knowledge about the metabolism of this element as well as its biological role. In this review, we discuss omics approaches from the workflows to their applications that has been previously used to deep insight into the metabolism of dietary selenium. There is a special focus on selenoproteins, metabolomics responses in blood and tissues (e.g., brain, reproductive organs, etc.) as well as the impact on gut microbiota and its metabolites profile. Thus, we mainly reviewed heteroatom-tagged proteomics, metallomics, metabolomics, and metataxonomics, usually combined with transcriptomics, genomics, and other molecular methods.

Abbreviations: AEC, anion exchange chromatography; AF, affinity chromatography column; ApoE, apolipoprotein E; ApoEr2, apolipoprotein E receptor-2; CE, capillary electrophoresis; CEC, cation exchange chromatography; CSF, cerebrospinal fluid; GC, gas chromatography; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSeSG, glutathione (GSH)-conjugated selenide; HMDB, human metabolome database; HPLC, high performance liquid chromatography; HPLC-MS, high performance liquid chromatography with mass spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; IDA, isotopic dilution analysis; LA, laser ablation; MeSeCysSe, methylselenocysteine; mTOR, mammalian target of rapamycin; NMR, nuclear magnetic resonance spectroscopy; NMD, nutritional muscular dystrophy; PCR, polymerase chain reaction; qRT-PCR, real-time quantitative reverse transcription polymerase chain reaction; RDA, recommended dietary allowance; rDNA, ribosomal deoxyribonucleic acid; RNA, ribonucleic acid; RP, reverse phase chromatography column; SeAlb, selenoalbumin; SEC-AF, size exclusion-affinity chromatography; SeCN, selenocyanate; SeCys, selenocysteine; SeCys2, selenocystine; SeCysta, selenocystamine; SeHLan, selenohomolanthionine; SELENOP, selenoprotein P; SeMet, amino acid methionine; SeSug 3, methyl-2-amino-2-deoxy-1-seleno-β-D-galactopyranoside; SeSug1, 1β-methylseleno-*N*-acetyl-D-galactosamine; SeSug2, methyl-2-acetamido-2-deoxy-1-seleno-β-D-glucopyranoside; SPB, Se-binding proteins; SUID, species-unspecific isotope dilution; TMSe, trimethylselenonium ion; TRXR, thioredoxin reductase; UL, tolerable upper limit.

Ana Arias Borrego and Belén Callejón-Leblic contributed equally.

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KEYWORDS
heteroatom-tagged proteomics, metabolomics, metallomics, meta-omics, microbiota, selenium

1 | INTRODUCTION

Selenium (Se), a non-metal with several allotropes displaying metalloid properties, is a well-known health relevant nutrient. Se consumption at adequate doses is undoubtedly a health requirement. However, in humans, Se is required as a micronutrient with a recommended dietary allowance (RDA) in the range of 55–70 µg/day [1]. Studies of higher than normal Se intakes led to the establishment of 400 µg Se/day as the tolerable upper limit (UL) that is about eight-fold the requirement. Therefore, Se containing supplements in both, organic and inorganic forms, should be below three-fold the required amount, without exceeding the total daily selenium intake of an adult considering the averaged consumption plus the supplementation (200 µg Se/day) [2]. Nowadays, multi-omic approaches have turned into powerful tools to understand the biological responses to dietary Se being especially worthwhile when they are combined. Likewise, heteroatom-tagged proteomics allows determining the absolute concentration of selenoproteins and selenometabolites in biofluids and tissues using Se as a 'tag' in an elemental sensitive detector like inductively coupled plasma mass spectrometry (ICP-MS) [3]. To delve into the responses of dietary Se, the application of this omic make possible the evaluation of Se in vitro bioaccessibility, defined as the proportion of Se soluble in the intestine. Besides, it is possible to evaluate the in vivo bioavailability and bioactivity, that are the fraction of Se that reaches the systemic circulation or that are transformed into bioactive Se-containing molecules, respectively [4, 5]. In a broader context and very close to this omic, metallomics has been defined as the study of element distribution, equilibrium concentrations of free metal ions or as a free element content in a cellular compartment, cell or organism. It can be extended to the whole amount of chemical species (i.e., molecules or complexes containing the element, different isotopes or elements with different oxidation state [6]. Furthermore, metallomics is the study of the metallome, the interactions and functional links of metal ions and their species with metabolites, proteins, genes, and other biomolecules [7]. Otherwise, metabolomics, the omic closer to the phenotype, involve the measurement of hundreds of molecules with molecular mass lower than 1500 Da in different biofluids, tissues or gut contents that are the last mechanism of action related to the impact of dietary Se in the body [8, 9]. Moreover, proteomics enables the massive analysis of proteins, including selenoproteins, which could be biomarkers related to the impact of dietary Se in different tissues or biofluids. Transcriptomics and genomics make possible the efficient sequencing of complete genomes, but the main drawback is that alterations in gene expression is not directly connected to the final response to dietary Se. Finally, a meta-omic methodology comprises metataxonomics, metagenomics, metatranscriptomics, metaproteomics, and metabolomics. They cover the study of "meta"genomes, regions of the ribosomal RNA genes, transcriptomes, proteomes or metabolomes, which are mixtures of genes, regions of genes (16S rRNA region), transcripts, proteins or metabolites from several organisms [10]. Meta-omic methodologies pave the way to understand the impact of dietary Se in the microbiota and thus, the potential influence on other human niches and establishment of the specific axis: the "gut-brain axis" (GBA), the "gut-gonad crosstalk" or the "gut(enteromammary gland)-brain axis" [11].

2 | HETEROATOM-TAGGED PROTEOMICS AND METALLOMICS

2.1 | The role of selenoproteins and selenometabolites

The main biological functions of Se are related to selenoproteins, in which the amino acid selenocysteine (SEC) is encoded by the stop codon UGA, when the selenocysteine (SeCys) insertion sequence element is located in the mRNA. This is the case of selenoprotein P (SELENOP), the best biomarker of Se status in human serum [12]. This selenoprotein, produced in the liver and transported to the periphery, has key roles in the transport and homeostasis of Se [13]. SELENOP also possess antioxidant functions since it bounds to heparin and carbohydrates in the endothelium [14], reduces phospholipid hydroperoxides, it shields human astrocytes and endothelial cells from oxidative damage [15] as well as plasma proteins from nitration and oxidation [16]. Besides, SELENOP has key roles in neurological activity because this protein with its receptor apolipoprotein E receptor 2 (ApoER2) favors Se retention in brain compared to other organs and it has the same receptor than apolipoprotein E (ApoE), whose polymorphisms represent a genetic risk of Alzheimer's disease [17]. SELENOP affects Aβ and hyperphosphorylated tau aggregation, it has signaling functions though neuronal ApoER2 [18] and increases neuronal precursor cells in mice brain after supplementation with Se [19]. Other selenoproteins, like the major abundant selenoenzyme glutathione peroxidase (GPx) or thioredoxin reductase (TRXR), present important antioxidant functions [20]. Besides the 25 selenoproteins that have been described in humans, there are also Se-containing proteins. This is the case of the Se transporter selenoalbumin, (SeAlb), in which Se replaces the sulfur in the amino acid methionine (SeMet) as well as Se-binding proteins (SPB), like SBP1, in which Se is strongly bound to a Cys residue.

Moreover, selenometabolites, which encompass inorganic selenium, selenoamino acids, and other organic Se-containing compounds with

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a molecular mass below 1500 Da, have been recognized as significant factors in nutrition and health [5, 21, 22]. Notably, among these compounds, inorganic Se (such as selenite, ^{IV}Se, and selenate, ^{VI}Se) exhibits higher acute toxicity compared to SeMet or selenium yeast, and also lower bioavailability when obtained from dietary sources [23]. Otherwise, organic forms of Se are considered more toxic during long-term exposure [21]. Thus, supplementation with Se is difficult because the dose and the chemical form of Se should be selected carefully. Likewise, it has been reported that Se may have a beneficial effect at a low dose and an inhibitory or toxic effect at a high dose [22]. Besides, Se is also known to have narrow range of concentration separating chronic conditions of deficiency and toxicity [23].

2.2 | Analytical approaches for selenoproteins and selenometabolites determination in plasma/serum

Hyphenated ICP-MS, that is coupled to high performance liquid chromatography (HPLC) or capillary electrophoresis (CE), allows determining selenometabolites and selenoproteins. Instead of a molecular detector, Se-containing molecules are indirectly determined measuring the heteroatom Se (or any atom different to C, H, N, O or F) as a "tag" in the atomic detector (ICP-MS) after the separation of the Se-containing biomolecules. This intact protein analysis is more sensitive and selective than the classical proteomic approaches based in the use of molecular mass spectrometry due to the use of an atomic mass spectrometric detector, especially with instruments equipped with triple quadrupole or collision/reaction cells [20]. In addition, the absolute quantification of proteins does not require protein standards of difficult availability and selenoproteins can be quantified by isotopic dilution analysis (IDA) by the addition of isotopically enriched Se and using signal ratios instead of signal intensities [24].

Regarding the sample, serum/plasma is easy to obtain and analyze because it can be directly injected, after filtration, into the HPLC [12, 25–28] and it can be very useful to delve into the responses to dietary Se. The validation of the method with certified reference materials is not yet possible because they are not available, but several authors reported the concentration of selenoproteins with different methodologies in the BCR-637 human serum certified for total Se [12, 26, 28–31]. In human serum/plasma, up to 90% of total Se can be quantified by using this methodology (Figure 1A) and the detectable species are GPx (~15%–20% of total Se), SELENOP (>50% of total Se), and SeAlb (~15%–20%) (Figure 1B) [32, 33]. These three selenoproteins are considered good markers for the assessment of Se status in human plasma/serum [34]. Using a specific rearrangement of the chromatographic columns, based in a column switching method combining SEC and affinity chromatography column (AF) before the ICP-MS, a peak of total selenometabolites (~0%–8% of total Se in human serum) can also been separated and quantified (Figure 1A) [26, 28].

Other configurations of chromatographic columns for selenoproteins determination by heteroatom-tagged proteomics has been previously described and compared [29, 33]. Besides, the accurate quantification of SELENOP in plasma has been described by using isotopically enriched selenopeptides and species-specific IDA before HPLC-ICP-MS-MS [35].

The methodology for selenoproteins and total selenometabolites based on size exclusion-affinity chromatography (SEC-AF)-ICP-MS has also been optimized for human milk (Figure 1B). Due to the presence of selenocystamine (SeCysta) in human milk and its affinity for heparin contained in the AF chromatographic column used for the retention of SELENOP, a specific rearrangement of the column switching method for human serum was needed for human milk. The new method allows separating GPx, SeCysta, other selenometabolites eluting in one peak, SeAlb and SELENOP, being the last identified for the first time in human milk [36].

The determination of selenometabolites in human serum/plasma and urine can also be performed by HPLC coupled to ICP-MS using reversed phase [27, 37] anion (AEC) [37–39] or cation exchange chromatography (CEC) [37, 40]. Interestingly, several selenometabolites and selenoproteins have been determined in human serum [41] and cerebrospinal fluid (CSF) [41, 42] by AEC-ICP-MS and the identification of the Se-containing molecules was performed by 2D by SEC-AEC- and AEC-CE-ICP-MS. Using this method, the authors determined in only one chromatographic run ^{IV}Se, ^{VI}Se, SeMet, SeCys, TRXR-bound Se (Se-TrxR), GPx (EC 232-749-6)-bound Se (Se-GPx), and SeAlb. The combination of HPLC-ICP-MS with high performance liquid chromatography with mass spectrometry (HPLC-MS) is very adequate for the confirmation of selenometabolites [43] and selenoproteins [36]. Thus, selenometabolites have also been determined in urine after the ingestion of Se supplements by HPLC-ICP-MS combined with HPLC coupled to organic mass spectrometry [44].

A flow-chart (Figure 1A) shows a typical approach for the determination of selenoproteins and total selenometabolites in serum/plasma by SEC-AF hyphenated to species-unspecific isotope dilution (SUID) ICP-MS (2D-SEC-SEC-AFxAF-ICP-MS) [26]. This configuration of chromatographic columns allows determining GPx, SELENOP, SeAlb, and total selenometabolites. Figure 1B shows a typical chromatogram obtained from human serum. Figure 1C shows a typical approach for the determination of selenoproteins, total selenometabolites, and SeCysta in human milk by a modification of the method above described for human serum [45]. Figure 1D shows a typical chromatogram obtained from human milk. Figure 1E shows a typical chromatogram of selenometabolites in human serum by reverse phase chromatography column (RP)HPLC-ICP-MS using a methodology previously described [46]. The main shortcoming of HPLC-MS for selenoproteins is the application to biological tissues because, unlike plasma/serum can be directly injected after filtration, tissues require the quantitative extraction of selenoproteins. Likewise, there is not yet a sample preparation method with enough recovery for selenoproteins in tissues nor a chromatographic method to separate the selenoproteins previously reported in that samples by polymerase chain reaction (PCR), western blot o enzymatic assays. In this case, an alternative could be selenotranscriptomics that is very sensitive and can be easily applied to tissue extracts. This method has been applied to mice brain tissue after Se-supplementation for the determination of the whole selenotranscriptome in brain

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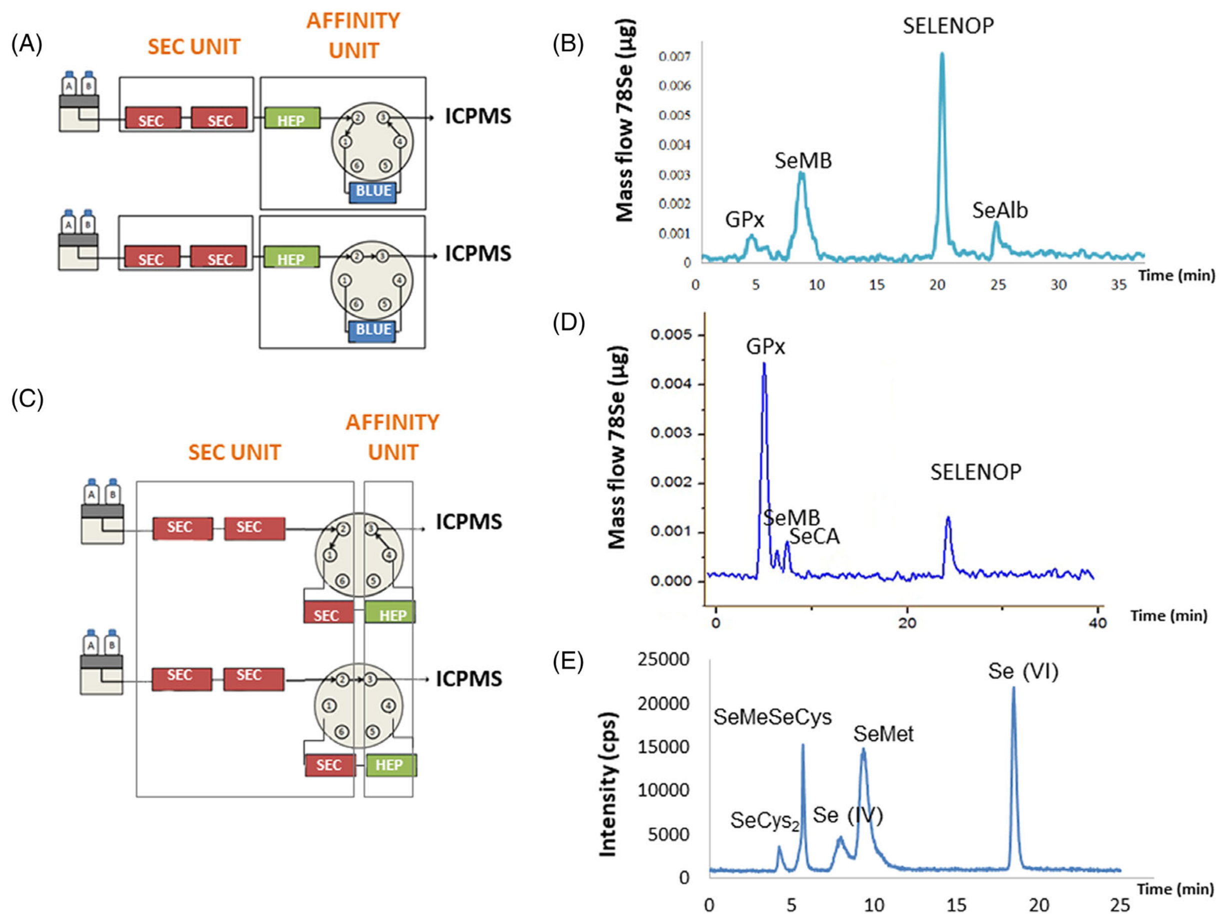

FIGURE 1 (A) Analytical method for the absolute quantification of selenoproteins and total selenometabolites in human plasma/serum. Upper part: the mobile phase pass through the two selenocysteine (SeCys) columns, then glutathione peroxidase (GPx) elutes and it is detected in the inductively coupled plasma mass spectrometry (ICP-MS), because it does not have affinity for the affinity chromatography columns (AFs). After that selenoprotein P (SELENOP) is retained in the first AF column and selenoalbumin (SeAlb) in the second and selenometabolites elutes from the SEC columns being detected in the ICP-MS lower part: after that, the column switching valve changes the position to isolate the retained SeAlb, the mobile phase change in composition, SELENOP elutes from the first AF column and it is detected in the ICP-MS. The column switching valve changes again (upper part) and SeAlb elute. (B) Typical chromatogram obtained for selenometabolites and selenoproteins in human serum. The sample has been fortified with Se (100 ng g^{-1}) to show the retention time. (C) Analytical method for the absolute quantification of selenoproteins and selenometabolites in human milk. Upper part: the mobile phase pass through the two SEC columns, then GPx elutes and it is detected in the ICP-MS, because it does not have affinity for the AF column. After that SELENOP is retained in the AF column. Lower part: then, the column switching valve change the position to avoid the retention of selenocystamine (SeCysta) in the AF column that is isolated with SELENOP retained. After that, SeCysta and selenometabolites elute and they are detected in the ICP-MS. Upper part: the column switching valve change again for the elution of SELENOP. (D) Typical chromatogram of selenoproteins, SeCysta and other selenometabolites in human milk after the extraction by ultracentrifugation. (E) Typical chromatogram of selenometabolites in human serum by high performance liquid chromatography-reverse phase chromatography column (HPLC-RP)-ICP-MS.

corresponding to the 24 selenoprotein genes [47]. Otherwise, the drawback of transcriptomics is that there is not a direct connection between the alterations in gene expression and the selenoproteins levels.

Another possibility for the determination of selenoproteins is the hyphenation of laser ablation (LA) with ICP-MS. With this analytical method, the selenoproteins are separated as a function of their iso-electric point using iso-electrofocusing electrophoretic strips and then, detected by LA-ICP MS. This method has been applied for the determination of Gpx1, Gpx4, TXNRD1, TXNRD2, and SELENOF in human cell lines [48].

Previous studies related with the determination of selenometabolites and/or selenoproteins in mammals after Se-supplementation (Table 1). These studies reported very valuable knowledge about the metabolism and mode of action of selenocompounds. A number of studies reported the metabolism of Se in urine and serum after supplementation with Se-containing capsules containing different chemical species of Se [5, 25 ,37, 38, 44, 47, 49–57]. In a study comparing different commercial Se-containing capsules with different chemical species of Se, the authors concluded that selenosugar 1 (1β-methylseleno-*N*-acetyl-D-galactosamine [SeSug1]) was present in human serum after all the treatments. Also, they concluded

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TABLE 1 Reported studies that have determined selenoproteins and/or selenometabolites in different model organisms after supplementation with Se.

Se in the supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Selenometabolites and/or selenoproteins determined in the body	Analytical method	Reference
^{VI}Se, ^{IV}Se, SeMet, MeSeCys, selenized yeast	Capsule/tablet	Human	Serum	Selenosugar 1, SeMet, TMSe, selenite, MeSeCys	HPLC-MS	[44]
			Urine	Selenosugar 1 and 3, SeMet, TMSe, SeMet		
^{VI}Se	Se-enriched microalga	Mice	Serum	GPx, SELENOP, SeAlb, total selenometabolites	(RP) HPLC-ICP-MS	[5]
^{IV}Se	Se-enriched chow	Mice	Serum	GPx, SELENOP, SeAlb, total selenometabolites	2D-SEC-SEC-AFxAF-ICP-MS	[49]
^{IV}Se	Se-enriched chow	Mice	Testicles	GPx, SELENOP, SeAlb, total selenometabolites	2D-SEC-SEC-AFxAF-ICP-MS	[50]
^{IV}Se, SeMet	Se-fortified water	Rhesus Monkey	Muscle, liver, plasma, erythrocytes, hair	Total Se, GPx activity, Se fractionation	SEC/atomic absorption spectrometry	[51]
^{IV}Se	Se-enriched chow	Mice	Brain	Whole selenotranscriptome (25 selenotranscripts)	qRT-PCR	[47]
^{IV}Se	Se-enriched spirulina	Rats	Plasma, urines, liver, brain, kidney, heart, and soleus	Total Se and antioxidant enzyme activities (GPx)	ICP-MS, antioxidant enzyme activities, and RT-PCR	[62]
Selenized yeast reference material (SELM-1)	Se-yeast supplement	Human	Plasma	SeMet, SeSug-1, MeSeCys, SeALB	HPLC-ICP-MS and HPLC-ESI-MS/MS	[25]
^{IV}Se, L-selenomethionine, or DL-selenomethionine	Se-fortified water	Human	Urine	SeMet, SeSug 1, 2, and 3	HPLC-ICP-MS and HPLC-MS	[38]
Se-containing fertilizers	Se-enriched potatoes	–	Potato flesh and skin	SeMet, SeMeCys	(RP) and (AEC) HPLC-ICP-MS, HPLC-ESI MS/MS	[52]
^{IV}Se, selenized yeast	Capsule/tablet	Human	Urine	^{VI}Se, SeSug 1 and 3, TMSe	(AEC) HPLC-ICP-MS	[58]
^{VI}Se	Capsule/tablet	Human	Serum	MeSeCys, ^{VI}Se, SeSug 1 and 3, unknowns	(RP) HPLC-ICP-MS	[37]
^{VI}Se	Se-enriched leek and kenaf, Se-enriched yoghurt, tablets	Human	Stomach, small intestine and colon	SeMet, SeCys2, MeSeCys	(RP) HPLC-ICP-MS	[53]
^{VI}Se, ^{VI}Se	Se-fortified serum	Human/mice	Plasma/serum	GPx, SELENOP, SeAlb	3D/SE-AF-AEC-HPLC	[57]
^{82}Se-selenite and -selenate	Intravenous administration	Rat	Plasma	SeAlb	SEC-ICP-MS	[54]
			Urine	^{VI}Se		
			Liver	Se-methyl-*N*-acetyl-selenohexosamine (selenosugar)		

(Continues)

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TABLE 1 (Continued)

Se in the supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Selenometabolites and/or selenoproteins determined in the body	Analytical method	Reference
^{IV}Se	Torula yeast diet	Rat	Liver	SBP1, SBP2, GPx1	SEC-ICP-MS and HPLC-MS	[55]
^{IV}Se, ^{VI}Se, SeCN, SeMet, MeSeCys, SeHLan, SeCys2, SeSug1, or TMSe	Intravenous and oral administration	Rat	Urine	^{IV}Se, ^{VI}Se, SeCN, SeMet, MeSeCys, SeHLan, SeCys2, SeSug1, or TMSe	SEC-ICP-MS, enzyme activity, and western blott	[63]
			Serum	GPx3, SELENOP, SeAlb		
^{76}Se-MeSeCys, ^{77}Se-SeMet, and ^{82}Se-selenite	Oral administration	Rat	Liver, kidneys, heart, brain, testis, spleed, páncreas, red blood cells, urine, serum	GPx, SELENOP, TMSe, SeMet, MeSeCys, GSSeSG, selenosugars, inorganic Se	Selenometabolomics	[60]
SeMet, SeCN, SeCys2, TMSe, and ^{IV}Se	Oral administration	Rat	Serum	GPx3, SELENOP, SeMet, MeSeCys, SeCys2, SeCN, TMSe, SeHLan, and SeSug 1	LC-ICP-MS and SEC-ICP-MS	[59]
Seleno-lentinan (HNO_3–Na_2SeO_3)	Oral administration	Mice	Pancreas and body	GPx and gut microbiota composition	Enzyme activity	[64]
^{IV}Se and $HgCl_2$	Oral (Se) and subcutaneous (Hg) administration	Mice	Liver, kidneys, serum	GPx, SELENOP, SeAlb, total selenometabolites	2D-SEC-SEC-AFxAF-ICP-MS	[65]
^{IV}Se	Cell growth	Human cell lines	Hek293 (kidney), HepG2 (liver), HaCaT (skin), and LNCaP (prostate)	Sep15, GPx1, GPx4	LA-ICP MS	[66]
^{IV}Se and $CdCl_2$	Oral (Se) and subcutaneous (Cd) administration	Mice	Plasma	GPx, SELENOP, SeAlb, total selenometabolites	2D-SEC-SEC-AFxAF-ICP-MS	[56]

GPx, glutathione peroxidase activities; GSH, glutathione; GSSeSG, GSH-conjugated selenide; MeSeCys, Se-methylselenocysteine; SeCN, selenocyanate; SeCys2, selenocystine; SeHLan, selenohomolanthionine; SeMet, selenomethionine; SeSug1, 1β-methylseleno-*N*-acetyl-D-galactosamine; SeSug2, methyl-2-acetamido-2-deoxy-1-seleno-β-D-glucopyranoside; SeSug3, methyl-2-amino-2-deoxy-1-seleno-β-D-galactopyranoside; TMSe, trimethylselenonium ion.

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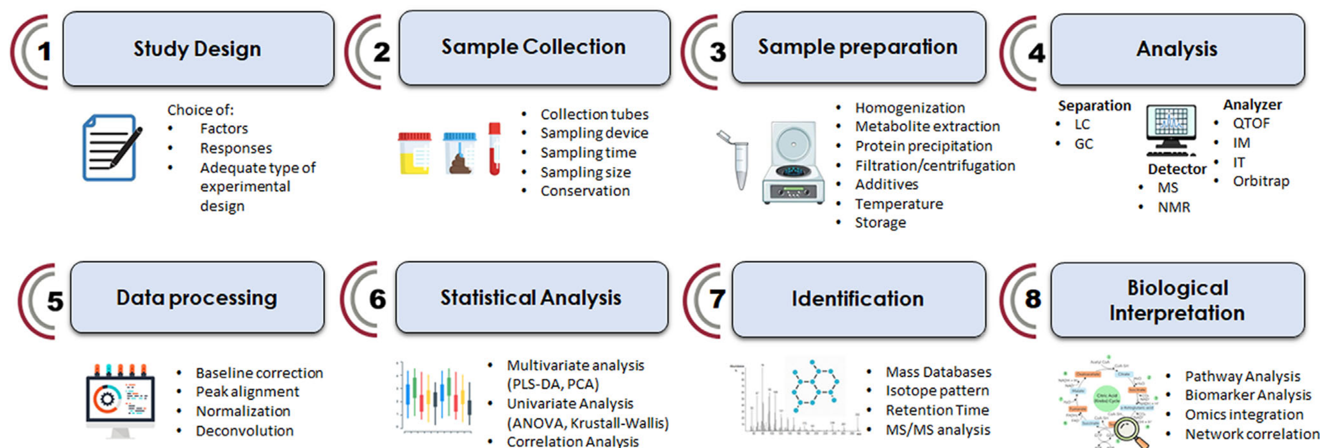

FIGURE 2 Typical metabolomics workflow showing the different steps of the analysis.

that it was the major selenometabolite in human urine except for capsules with selenate (^{VI}Se). Other selenometabolites like ^{IV}Se, methyl-2-amino-2-deoxy-1-seleno-β-D-galactopyranoside (SeSug 3), and trimethilselenonium ion (TMSe) have been determined in human urine and selenomethylselenocysteine, SeSug3, and several unknowns in human serum after Se-supplementation with capsules [58]. Using other Se-supplements (e.g., selenized yest, Se-fortified water with ^{IV}Se or DL-SeMet) other authors reported the presence of SeMet and methyl-2-acetamido-2-deoxy-1-seleno-β-D-glucopyranoside (SeSug2) among the above commented selenometabolites [25, 38]. Interestingly, using LC-ICP-MS and SEC-ICP-MS the authors reported the presence of GPx, SELENOP, SeMet, MeSeCys, selenocystine (SeCys2), selenocyanate (SeCN), TMSe, selenohomolanthionine (SeHLan), and SeSug 1 in rat serum after oral administration with SeMet, SeCN, SeCys2, TMSe, and IVSe [59]. Thus, the metabolism of Se is very dependent on the chemical form in the supplement. Likewise, using different chemical forms of Se with Se-enriched isotopes in rats, the authors concluded that the incorporation of Se into SELENOP follows the order: ^{IV}Se > MeSeCys > SeMet [60]. Moreover, ^{IV}Se was taken up quickly by red blood cells where glutathione reduced it to selenide, being later transported to the plasma, where it bounds to albumin to be finally transported to the liver. Otherwise, ^{VI}Se was either excreted into the urine or taken up directly by the liver [61].

Regarding the determination of selenoproteins using HPLC-ICP-MS several works reported the presence of GPx, SELENOP, and SeAlb in mice [5, 49], human [57], and rat serum [63] after Se-supplementation. Selenoproteins have been determined in biological tissues using ICP-MS [67–69].

In addition, Se is a well-known antagonist against several pollutants [70] and previous studies have also been developed to determine selenoproteins and selenometabolites after the exposure to Hg [71, 72], Cd [71], As [71] without Se-supplementation. Also, the distribution of elements among the different mice organs and plasma after the exposure to Cd and Se-supplementation has been reported [73]. SeCN, Se-methylselenocysteine (MeSeCys), selenomethionine (SeMet), SeHLan, SeCys2, SeSug1, SeSug2, methyl-2-amino-2-deoxy-1-seleno-β-D-galactopyranoside (SeSug3), and trimethylselenonium ion (TMSe), glutathione (GSH)-conjugated selenide (GSSeSG), Se-methylselenocysteine (MeSeCys), SeCys2, and GPx activities.

3 | METABOLOMIC APPROACHES TO DELVE INTO THE RESPONSES TO DIETARY SELENIUM

3.1 | Metabolomic workflow

Metabolomics is a powerful tool providing valuable information about the response to dietary Se by measuring hundreds of molecules that are altered in biofluids, tissues or gut contents after Se-supplementation or under Se deficiency. A typical metabolomic workflow is shown in Figure 2. The first step is the selection of the model organism and after that, metabolites are extracted using a non-selective sample preparation method to recover as much metabolites as possible from the sample under study. The sample preparation should ensure the extraction of polar and non-polar metabolites using a single step [74] or a classical two-step approach using aqueous and organic phases separately [75]. The main objective is to achieve a rich and broad coverage of a wide range of endogenous and exogenous metabolites in a single profile that represents the impact of dietary Se. After the extraction, several analytical techniques have been shown to provide good results for global analysis such as gas chromatography (GC), HPLC-MS or CE coupled to mass spectrometry as well as nuclear magnetic resonance spectroscopy (NMR) [76–81]. It has been reported that NMR is reproducible, fast, the sample preparation is easy and there are comprehensive databases available for metabolite annotation [82]. These advantages besides its non-destructive character and small sample consumption have become NMR as a valuable tool for the analysis of a great number of samples in which the sample amount is limited. Otherwise, MS is highly sensitive and specific and provides good metabolite coverage for low concentrated compounds. Moreover, MS allows quantifying the compounds of interest by targeted metabolomics [83].

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TABLE 2 Metabolomics studies in biofluids, tissues, and gut contents after selenium supplementation.

Se-supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Impact determined	Analytical method	Reference
^{IV}Se	Se deficient diet	Broilers	Muscle	↓GPX1, SELENOW, TXNRD1-3, DIO1, SELENOF, SELENOH, SELENOI, SELENOK, SELNOM, and SELENOU.	Histopathology, transcriptomics and metabolomics assays (LC-MS)	[103]
				320 Transcripts and 33 metabolites significantly altered.		
				NMD by the dysregulation of one-carbon metabolism.		
Nanoselenium	Nanoselenium *Siraitia grosvenorii*	Mice	Liver and gut content	Positive effect on obesity by reducing the contribution acetyl-CoA in the TCA cycle.	16S rRNA sequencing and metabolomics (LC-QTRAP-MS)	[85]
				Increased gut microbiota diversity and modulated their composition		
^{IV}Se and Cd	Drinking water	Mice	Lung	Prevented Cd accumulation in lung and linked responses at metabolomic and transcriptomic levels.	Cd concentration, transcriptomics and metabolomics (LC-LTQ-Velos Orbitrap-MS)	[90]
^{IV}Se	Drinking water	Mice	Liver	Alters hepatic fatty acid and energy metabolism and increases the body mass.	Se concentration, activity of selenoproteins, GSH, redox state, gene expression, and high-resolution metabolomics (LC-LTQ-Velos Orbitrap-MS).	[91]
Non-specified	Se-deficient and regular diets	Mice	Serum	15 Altered metabolites.	Untargeted metabolomics (^{1}H NMR and GC-MS)	[92]
^{IV}Se	Se-supplemented chow	Mice	Brain and gut content	31 Metabolites altered in brain. Specific associations with gut microbiota.	Untargeted metabolomics (GC-MS and RP-UHPLC-QTOF-MS), selenotranscriptomics	[47]
^{IV}Se and $CdCl_2$	Se-supplemented chow and Cd subcutaneously administered	Mice	Liver, kidneys, brain, testes, serum, lung	Se and Cd alters the homeostasis of metals in the organs and the metabolome.	Untargeted metabolomics (GC-MS and DI-QTOF-MS) and metals distribution	[73]
Combined Se-yeast and folate (Se-FA)	Normal and low Se-FA doses	Mice	Blood and brain	Restored blood lipid levels and brain lipidomic profile that are involved in the reduction of Aβ production and tau hyperphosphorylation.	ELISA, immunoblotting and immunostaining, electrophysiological analysis and untargeted metabolomics (UHPLC-MS)	[97]
Se-yeast	Se-supplemented diet	Mice	Hippocampi and cortices	Promising diet for prevention and treatment of Alzheimer disease.	Se levels, SOD activity, MDA levels, immunofluorescent staining, histological analysis, and untargeted metabolomics (1H MRS)	[98]
				Ameliorated the cognitive impairment.		

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TABLE 2 (Continued)

Se-supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Impact determined	Analytical method	Reference
DDE and ^{IV}Se	Se and DDE supplemented chow	Mice	Liver, kidneys, and brain	70 Altered metabolites.	Untargeted metabolomics (GC-MS and DI-QTOF-MS)	[93]
Sodium selenite	Se mildly low diet	Mice	Liver	Alteration of the amino acid metabolism in liver.	Trasnscriptomics and untargeted metabolomics (GC-TOF-MS)	[94]
				Elevated levels of glycine in the liver.		
Sodium selenite	Se deficient diet	Mice	Liver and brain	Reduced selenoprotein expression.	RNA sequencing, microRNA analysis, and untargeted metabolomics (LC-Q-Orbitrap-MS)	[95]
				Reduced amino acid levels and elevated mononucleotides.		
				Pro-longevity mechanisms.		
Sodium selenite or SeMet	Se-supplemented chow	Mice	Serum, liver, spleen, colon, fecal content, jejunum, and mesenteric lymph node	Affected the intestinal immune responses and gut barrier depending of the form of Se.	mRNA expression, metabolomics (LC-LTQ Orbitrap-MS) and proteomics	[96]
				Alterations in the fecal metabolomic and jejunum proteomic profiles of mice depending on the form of Se.		
Se nanoparticles	Se nanoparticles	Mice	Gut content	Modulated the gut microbiota and its metabolism, improving diquat-induced toxicity	16S rDNA gene sequencing analysis and untargeted metabolomics (LC-QTOF-MS)	[86]
^{IV}Se and a mixture of pollutants	Se-supplemented chow	Mice	Brain and gut content	49 Metabolites altered in brain after the exposure to pollutants.	16S rDNA gene sequencing analysis and untargeted metabolomics	[87]
				Several metabolites altered by pollutants were antagonized by Se.		
				Numerous associations between gut microbiota and brain metabolites.		
^{IV}Se and a mixture of pollutants	Se-supplemented chow	Mice	Serum and gut content	Associations between serum selenoproteins and gut microbiota.	16S rDNA gene sequencing analysis, untargeted metabolomics (GC-MS and RP-UHPLC-QTOF-MS), arsenic speciation, selenoproteome quantification	[88]
				Impact in the arsenic metabolization.		
^{IV}Se	Se-supplemented chow	Mice	Gut content	Key association between Se intake-microbiota-metabolites	16S rDNA gene sequencing analysis and untargeted metabolomics (GC-MS and RP-UHPLC-QTOF-MS)	[89]

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TABLE 2 (Continued)

Se-supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Impact determined	Analytical method	Reference
SeMet	SeMet addition	HepG2 cells	Cells	Promoted the proliferation of HepG2 cells, the transcription of selenoproteins, and the production of most amino acids.	Untargeted metabolomics (^{1}H NMR)	[104]
^{IV}Se	Se deficient and regular chows	Procapra przewalskii	Serum	86 Metabolites altered.	Untargeted metabolomics (LC-QTOF-MS)	[108]
SeMet	SeMet-supplemented diet	Zebrafish (*Danio renio*)	Brain and mithochondria	It could enhance adverse pathways for neurotransmitters and behavior.	Targeted metabolomics (UHPLC-QTRAP-MS/MS), histopathological, and targeted transcriptional endpoints	[109]
Se and coenzyme Q10 (SeQ10)	Tablets, capsules (SelenoPrecise)	Elderly humans	Plasma	95 Identified metabolites, 19 were significantly decreased after 18 months of intervention	Untargeted metabolomics (GC-TOF-MS)	[110]
^{IV}Se and SeMet-yeast	Se-supplemented diet at two levels	Atlantic salmon (Salmo salar)	Liver	Oxidative stress and altered lipid metabolism for both organic and inorganic Se at high levels.	Untargeted metabolomics (GC-MS and UPLC-LQT-MS)	[112]
SeMet	Se-supplemented and regular shows	Pigs	Liver	High levels induced hyperglycemia and hyperinsulinemia linked with the elevation of lipid synthesis and the suppression of sugar metabolism.	Targeted metabolomics (LC-Tripled Quad-MS)	[100]
Sodium selenite, selenized yeast, and soybean protein-chelated Se	Se-supplemented diet	Pigs	Blood and liver	22 Hepatic metabolites linked with lipid and cellular antioxidant metabolism.	Total and differential blood cell counts, untargeted metabolomics (GC-TOF-MS)	[102]
				Organic Se enhanced endogenous antioxidant activity.		
SeMet	Se-deficient and regular diets	Pigs	Muscle	Impact on redox, energy metabolism, and inflammation.		
Induced muscle dystrophy	Untargeted metabolomics (RP-UHPLC-Q-Orbitrap-MS), total Se concentration, genomics, trasncriotomics, lipidomics	[99]				
Non-specified	Se-deficient and Se-adequate diet in corn and soybeans	Pigs	Plasma and liver	Altered metabolic, proteomic and transcriptomic profile in dietary Se deficiency-induced hepatic disease.	Se content, redox parameters, cytokines, selenoprotein mRNA expression analysis, targeted metabolomics (LC-RP-TSQ), untargeted lipidomic (RP-UHPLC-QTOF-MS), proteomics, and transcriptomics	[101]

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TABLE 2 (Continued)

Se-supplement	Type of supplement	Model organism	Biofluid or tissue analyzed	Impact determined	Analytical method	Reference
				Se deficiency induced a redox imbalance by regulating selenoproteins.		
				The TCA cycle shifted to a glutamine catabolism metabolism with Se deficiency.		
Inorganic selenium	Standard diet, selenium-deficient diet and nano-Se supplemented diet	Rats	Serum and liver	Mitophagy regulated by the mTOR signaling pathway plays a dual protective role in liver fibrosis associated with Se.	Se-content and untargueted metabolomics (UHPLC-TOF-MS)	[105]
				Nano-Se supplements could reduce or prevent the development of liver fibrosis.		
Selenized glucose (SeGlu)	Drinking water	Rats	Feces, semen, and blood	SeGlu improved the sperm motility and viability, reduced the abundance of harmful bacteria, and enhanced the serum metabolome.	Histopathology, metagenome sequencing, and untargeted metabolomics (LC-Q-Orbitrap-MS)	[106]
Se nanoparticles or sodium selenite	Low and higher Se doses by oral gavage	Rats	Urine	Increased decenedioic acid and hydroxydecanedioic acid for both Se nanoparticules and selenite, but dipeptides were only increased for selenite.	Se-content and untargeted metabolomics (microTOFq time-of-flight-MS)	[107]
				Altered fatty acid and protein metabolism.		
Sodium selenite	Se-supplemented diet	Catfish	Blood and intestine	Affected the occurrence regularity of all small molecular metabolites and the changes of gut microbiota composition of P. fulvidraco.	Antioxidant ability analysis, 16S rRNA analysis, and untargeted metabolomics (UPLC-TripletOF-MS)	[113]
Non-specified	Supplemented diet of vitamins ADE, zinc, and Se	Donkey	Follicular fluid	Promoted follicle development, maturation, and ovulation rate through the interaction of genes and metabolites of the ovarian steroidogenesis and mineral absorption.	Transcriptomic and untargeted metabolomics (UHPLC-QTOF-MS)	[111]

GSH, reduced glutathione; HPLC, high performance liquid chromatography; NMD, nutritional muscular dystrophy; mTOR, mammalian target of rapamycin; RP, reverse phase chromatography column.

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After the analysis, a good classification of the groups of samples under study is expected and then, metabolites responsible of that classification can be identified/annotated by tandem mass spectrometry or databases (e.g., METLIN [http://metlin.scripps.edu] and human metabolome database [HMDB, http://hmdb.ca]). After that, a relative quantification of the metabolites can be performed (i.e., fold changes values) as well as the pathway impacts [84].

3.2 | Metabolomic studies related to the impact of dietary selenium: Multi-omics data integration

Untargeted metabolomic analysis after Se supplementation have been performed using mice models [47, 73, 85–98], pigs [99–102], broilers [103], cells [104], rats [105–107], gazelle [108], zebra fish [109], humans [110], donkeys [111], salmon [112], and catfish [113]. These studies reported a wide range of altered metabolites after Se supplementation focused on liver [73, 91, 94–96, 100–102, 105, 112] and plasma/serum metabolism [73, 92, 96, 101, 105, 108, 110], but also in muscle [99, 103], kidneys [73, 93], testes [73], lungs [73, 90], spleen [96], blood [97, 102, 106, 113], urine [107], feces or fecal/gut content [47, 96, 106], semen [106], follicular fluid [111], brain [47, 73, 93, 97, 109], and brain sections [98]. A summary of the metabolomics studies reported after Se supplementation using different analytical platforms is shown in Table 2. As can be seen, metabolomics is usually combined with transcriptomics [47, 90, 94, 99, 101, 103, 109, 111], histopathology [98, 103, 106, 109], metallomics [73, 90, 91, 98, 99, 105, 107], proteomics [96, 101], enzymatic activities [91, 97, 98], or targeted metabolomics [100, 109]. Several studies focused on metataxonomics and gut metabolomics [95, 96, 101, 106, 113]. Metataxonomics by means of targeted amplicon sequencing, mainly targeted to a specific region of the hypervariable 16S rRNA gene [114], is considered nowadays the current standard for microbial communities profiling. Otherwise, gut metabolomics allows identifying the metabolites produced by the gut microbiota [89] that could be involved indirectly in the gut-brain crosstalk through the neural pathway (e.g., neuroactive metabolites such as short chain fatty acids or butyrate, neurotransmitters) [115]. Therefore, it is believed that neuroactive dietary and microbial-produced metabolites could modulate the GBA to affect hormone secretion by enteroendocrine cells (EECs), the gut-barrier function, neurotransmitter production by gut microbiota and epithelium, as well as enteric glial signaling, which are of key importance to neurodegenerative diseases [115].

Likewise, it has been reported that Se-supplementation increases the diversity and richness of gut microbiota and changes the composition of the gut microbiota increasing some health-relevant taxa [49, 116, 117]. Also, Se impacts on plasma selenoproteome [49, 118], brain metabolome [47], and selenotranscriptome [47]. Numerous significant associations have been described between gut microbiota and gut metabolites [89], brain metabolites [47], or plasma selenoproteins [49] suggesting intertwined mechanisms. In antibiotic-depleted mice models, selenoproteins increased in plasma suggesting a competition between the host and the microbiota for Se intake [49]. In fact, around 1/4 of all bacteria have selenoproteins and thus, they require Se for their growth and metabolism [116]. Interestingly, Ogra and coworkers [59] reported that rat gut microbiota metabolized MetSeCys and SeCN to SeMet. They also studied evaluated in vivo the nutritional availability of nine naturally occurring selenometabolites concluding that gut microbiota might contribute to the Se nutritional availability [119]. Thus, there is a potential link between Se-supplementation-gut-microbiota-host metabolism and host-selenoproteome.

4 | CONCLUSION AND OUTLOOK

Selenium is an essential element for mammals, including humans, as it is a component of numerous enzymes. Its quantification in biological samples can be clinically important in situations of excessive or deficient intake. Otherwise, chemical speciation analysis of Se in different biofluids and tissues by combining a separation unit (e.g., GC, EC, and HPLC) to a sensitive and selective atomic detector like ICP-MS has been essential along time to understand the metabolism of Se in mammals. The combination of inorganic mass spectrometry for Se speciation with organic mass spectrometry using high-resolution mass spectrometers is also important for the unequivocal identification of selenometabolites as well as for the structural elucidation of new selenocompounds in food and biological samples. However, massive information about selenoproteins, metabolites, and gut microbiota are of key importance to fully understand the responses to dietary Se. Thus, heteroatom-tagged proteomics allows the absolute quantification of the plasma or serum selenoproteome. Otherwise, the sensitivity of transcriptomic techniques makes possible to evaluate the whole selenotranscriptome in tissues, which is of great interest in several organs like brain in connection with the neuroprotective effect of Se. Undoubtedly, the importance of human microbiota in nutrition requires the introduction of meta-omic methodologies to study the impact of dietary elements as Se. The potential interactions between Se, microbiota, and their associated metabolites, including metabolomics profile of other tissues and biofluids, would influence the human health.

AUTHOR CONTRIBUTIONS

This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

It is a review-type areticle and then, there is not any data related.

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