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Review

Mechanisms of selenium hyperaccumulation in plants: A survey of molecular, biochemical and ecological cues☆

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ABSTRACT

Background: Selenium (Se) is a micronutrient required for many life forms, but toxic at higher concentration. Plants do not have a Se requirement, but can benefit from Se via enhanced antioxidant activity. Some plant species can accumulate Se to concentrations above 0.1% of dry weight and seem to possess mechanisms that distinguish Se from its analog sulfur (S). Research on these so-called Se hyperaccumulators aims to identify key genes for this remarkable trait and to understand ecological implications.

Scope of review: This review gives a broad overview of the current knowledge about Se uptake and metabolism in plants, with a special emphasis on hypothesized mechanisms of Se hyperaccumulation. The role of Se in plant defense responses and the associated ecological implications are discussed.

Major conclusions: Hyperaccumulators have enhanced expression of S transport and assimilation genes, and may possess transporters with higher specificity for selenate over sulfate. Genes involved in antioxidant reactions and biotic stress resistance are also upregulated. Key regulators in these processes appear to be the growth regulators jasmonic acid, salicylic acid and ethylene. Hyperaccumulation may have evolved owing to associated ecological benefits, particularly protection against pathogens and herbivores, and as a form of elemental allelopathy.

General significance: Understanding plant Se uptake and metabolism in hyperaccumulators has broad relevance for the environment, agriculture and human and animal nutrition and may help generate crops with selenate-specific uptake and high capacity to convert selenate to less toxic, anticarcinogenic, organic Se compounds.

1. Background

The element selenium (Se) is characterized by several intriguing properties. It is required in trace amounts for the healthy metabolism of many life forms like microalgae, many Prokaryotes and animals, including mammals [1–3]. However, Se intake higher than a certain threshold may be harmful to these organisms. Inorganic Se anions can be pro-oxidants in cells, causing oxidative stress through depletion of intracellular glutathione; protein misfolding may also occur due to replacement of sulfur by seleno-aminoacids [4,5].

In humans, the window between deficiency and toxicity for Se is extremely narrow as compared to other micronutrients [6]. Selenium deficiency has been estimated to affect at least one billion people [7], especially in parts of China, North-West Europe, Australia, New Zealand, sub-Saharan Africa, Southern Brazil and parts of the USA [8,9,11]. This number may be growing, according to a moderate climate-change model scenario. Jones et al. [12] analyzed several environmental variables that may influence Se distribution worldwide and predicted that climate and soil organic matter changes will be responsible for a significant reduction of soil Se concentration in 2080–2099 as compared to a more recent situation (1980–1999), especially in agricultural regions.

Selenium concentration in soil, which mostly ranges between 0.01 and 2.0 mg Se ppm, primarily correlates with Se availability in the human diet [7]. Because plants represent the main portal for Se in the food web, Se biofortification programs are carried out to enrich staple crops with Se in order to overcome the Se-deficiency issue [13,14]. The success of these programs largely depends on understanding the mechanisms of Se uptake, assimilation, and tolerance by plants [3,13,14]. On the other side of the spectrum, in parts of the USA, Canada, China and India, soils occur that are rich in Se and named seleniferous soils; these contain 4–1200 ppm Se, which may be harmful to humans and livestock [8,15–17].

Se deficiency and toxicity concerns are not only related to Se concentration in soil, but also to its chemical form [3,9,11]. Selenium in soil and organisms can exist in different oxidation states and in various

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inorganic and organic forms, which can interconvert via chemical or biochemical processes [3,6]. Owing to its chemical similarity to S, conversion of inorganic Se into organic compounds can be realized via a non-specific route that involves the sulfur (S) assimilation pathway, as described for plants [18,19]. In addition, in organisms that have an essential requirement for Se, its conversion can be mediated by Se-specific enzymes, particularly its Se-specific incorporation into selenoproteins [6,20–23].

Evolutionary analyses support the assumption that essential Se metabolism in animals and certain algae (e.g. *Chlamydomonas reinhardtii*) evolved early and the environment played a crucial role in its further evolution, loss or persistence in different clades [3,24]. The loss of selenoproteomes in plants, fungi and some animals arguably happened via independent events and because of one or more undetermined environmental factors [1,24]. It has been hypothesized that aquatic life preserved Se metabolism in photosynthetic organisms, while terrestrial habitats dramatically reduced the metabolic dependence on Se because of its restricted availability [5,24].

Although lacking essential Se metabolism, plants can experience an array of beneficial properties from Se [25–27]. At low tissue concentrations, Se promotes plant growth and productivity and enhances resistance against certain types of abiotic stresses. With increasing tissue Se concentrations, Se also increasingly protects plants from herbivores and pathogens. Plants readily take up Se even though they do not require it, owing to the similarity of Se and S. The capacity of plants to accumulate Se is important for the food web, because plants represent the main entry of Se in the food chain.

The natural occurrence and distribution of Se in soil is a result of early geological soil formation and deposition, mainly as a response to volcanic activity in the Cretaceous period in the Mesozoic era (145 million years ago), in which ashes and gases containing Se were deposited in the ocean due to rain, largely ending up in the clay section of sedimentary rocks in the earth's crust from this geological period [28]. Reportedly, the average Se concentration worldwide is 0.44 mg kg^{-1} [28]. Soil Se concentration, composition and availability varies dramatically in relation to the physicochemical characteristics of soils. The accumulation of Se by plants is, to a large extent, influenced by Se concentration and phytoavailability in soils. In addition, differences between plant species exist with respect to their capacity to accumulate Se under the same environmental conditions [19,29,30]. Plant species thriving on seleniferous soils hold a special position in this respect, because they have evolved strategies to prevent Se toxicity while often accumulating high tissue Se concentrations [21,31–33].

Plants absorb Se using different types of transporters depending on the form of Se available for uptake [29,34–38]. The expression of these transporters and their kinetic properties and substrate specificity vary in the plant kingdom and contribute to plant adaptation to high-Se environments. Selenium is mostly present in soil in inorganic forms, primarily as selenate (SeO_4^{2-}) or selenite (SeO_3^{2-}), which are both soluble and thus readily available for plant uptake. However, plants can also take up organic Se compounds, especially in the form of selenoamino acids. They do not show substantial uptake capacity for the less bioavailable forms: elemental Se, metal selenide compounds or colloidal elemental Se [19,39]. Once inside plant cells, selenate can be assimilated into selenocysteine (Se-Cys) and selenomethionine (SeMet) through the biochemical pathway that is normally involved in sulfate reduction and assimilation [11,18,19,22,40]. The non-specific incorporation of these two Se-amino acids in proteins in the place of the analogs cysteine (Cys) and methionine (Met) causes the disruption of protein folding, which is considered the main cause of Se toxicity to plants [41]. In this respect, plants have evolved a range of strategies to mitigate Se toxicity, which include conversion of SeCys to elemental Se and alanine, methylation of SeCys and SeMet, and conversion of these compounds to volatile dimethyl(di)selenide (DMDSe) [18,42]. Accumulation of Se in plant tissues and production of methylated volatile Se species are both critical for Se cycling in the environment [43]. Selenium volatilization into the atmosphere by plants and microalgae may be responsible for a significant portion of Se fluxes and may contribute to the formation of seleniferous regions [43,44].

Plant species differ in their capacity to accumulate Se in their natural environment and to produce Se volatile compounds, as well as in their preferential strategy to avoid Se toxicity [3,30,45]. According to their capacity to accumulate Se, plants can be divided in three main categories: non-accumulators, which include species that accumulate less than 100 μg Se g^{-1} dry weight; secondary accumulators like *Brassica juncea* and *Brassica napus*, which can contain up to 1000 μg Se kg^{-1} dry weight, can thrive on both non-seleniferous and seleniferous soils, and their tissue Se concentration is directly indicative of the Se phytoavailability in the soil (Se-indicators); hyperaccumulators, such as certain species of the genera *Stanleya* (Brassicaceae) and *Astragalus* (Fabaceae), able to accumulate over 1000 μg Se g^{-1} dry weight in all organs (0.1–1.5%) when growing on seleniferous soils [3,19,30,46–49]. Within these three ecological groups, variation in Se concentration may also be observed between genera, species and even ecotypes within species [19,29,30,50–53].

The observed differences in physiology and biochemistry between these taxa in response to Se might have ecological significance and raises the question which benefits and potential constraints are associated with high concentrations of Se in plants, both physiologically and with respect to interactions with ecologic partners [3]. Selenium may enhance plant fitness via enhanced growth and abiotic stress resistance, protection from pathogens and herbivores, or via elemental allelopathy, i.e. competition towards other plant species that are sensitive to Se [3,19,32]. Plants that exhibit the fascinating trait of Se hyperaccumulation are of great interest in the field of Se research not only for intrinsic interest but because their study may benefit applications in Se phytotechnologies, i.e. biofortification and phytoremediation [3]. A particularly interesting trait in this respect is the capacity to accumulate Se specifically in the presence of high S concentration.

2. Selenium uptake in plants

2.1. Selenate transport and evidence for specific mechanisms of Se uptake in hyperaccumulators: model species Stanleya pinnata

Generally, selenate is more common and bioavailable than selenite in well-drained/oxidized and alkaline soils, while selenite is the prevalent water-soluble species in wetlands and anaerobic soils with a neutral to acidic pH [30,54,55]. Selenate is a chemical analog of sulfate (S), and thus it can enter the root cells and move throughout the plant via sulfate transporters [29,56]. Solid evidence for a role of the sulfate transport system in selenate movement across cell membranes derives from a study conducted in *Arabidopsis thaliana* selenate-resistant mutants by Shibagaki et al. [57] and El Kassis et al. [56]. SULTR1;2 in particular, i.e. the main group 1 root high affinity sulfate transporter involved in the active uptake of sulfate from the soil solution, was identified as the major portal for selenate entry into the plants, as *A. thaliana sultr1;2* mutants were more tolerant to selenate than wild-type plants and *sultr1;1* mutants [58]. In addition to SULTR1;2, under low external S concentration or in the absence of selenate/sulfate competition, another member of the group 1 root high affinity sulfate transporters, SULTR1;1, seems to mediate selenate transport as well [33,56,59,60]. Expression of these sulfate/selenate transporters is regulated by several factors, including the S status of the plant, the Se:S ratio in the plant organs and growth medium, and also the plant species [19,29,33,36,38].

Non-hyperaccumulators and hyperaccumulators often exhibit different expression levels of sulfate transporters in response to external Se and S availability, which in turn influences Se accumulation in their organs [29,33,36,38]. Hyperaccumulators typically show more abundant expression of sulfate transporters than non-hyperaccumulators (Fig. 1); while this explains their high Se concentrations, it does not

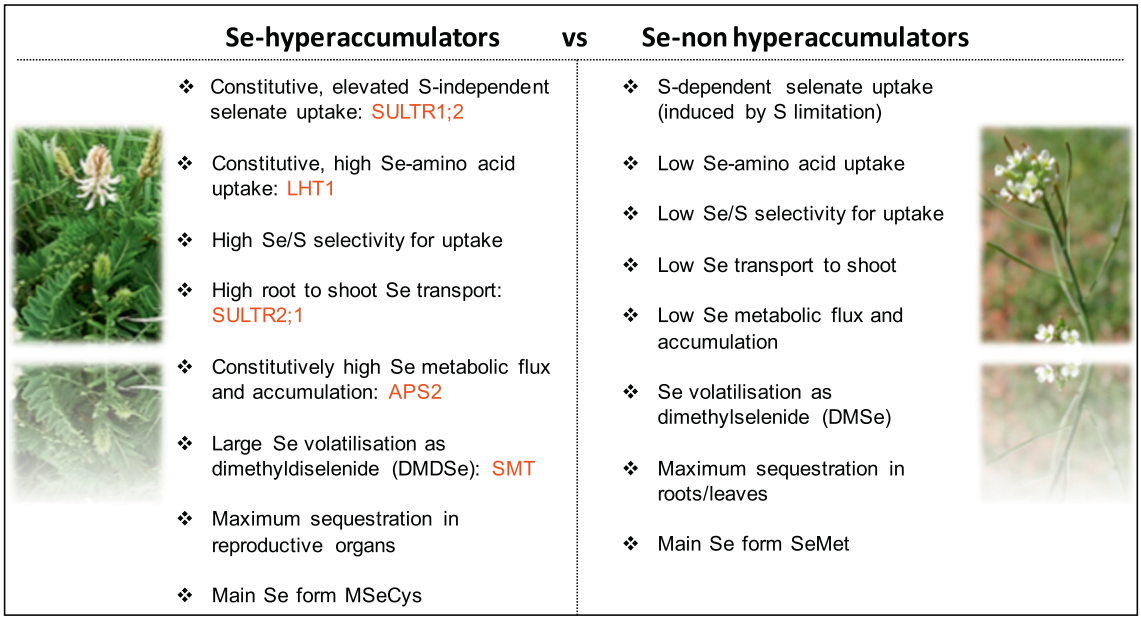

Fig. 1. Main physiological differences between Se-hyperaccumulators and non-hyperaccumulators plant species.

explain their high tissue Se:S ratio [36].

The Se-hyperaccumulator *Stanleya pinnata* has been recently reported to display greater root and shoot Se accumulation and less competitive inhibition by sulfate in the short (1 h) and long term (9 days) than non-accumulator *Stanleya elata* and accumulator *B. juncea* [33]. Specifically, selenate uptake rates for *S. pinnata* were not appreciably decreased by 100-fold excess sulfate over selenate in the short term, whereas they dramatically declined for non-hyperaccumulators. These results are well correlated with the expression of different sulfate transporter genes: *S. pinnata SULTR1;2* (root hairs, cortex and epidermis) and *SULTR2;1* (pericycle and xylem parenchyma) were constitutively expressed at very high levels in *S. pinnata*, and therefore may be responsible for higher selenate uptake and translocation to aerial parts, respectively, as compared to non-hyperaccumulators.

Constitutive expression of *SULTR2;1* homologs was previously observed in hyperaccumulator spp. of the genus *Astragalus* as well, while the transcript abundance of group 1 sulfate transporters was slightly affected by S starvation [36]. Also, *SpSULTR1;2* expression was not up-regulated in the absence of S as normally observed for sulfate transporters under S deficiency in non-hyperaccumulators (Figs. 1 and 2) [58,59,61]. Based on these findings, the two *Sultr* genes are likely crucial for the Se hyperaccumulation trait in *S. pinnata* [62–64]. The question why *SpSULTR1;2* does not show up-regulation in response to S limitation still remains to be elucidated, but it can be hypothesized that constitutive and elevated expression of this transporter might be in part the result of gene duplication events that induced elevated selenate uptake capacity and promoted the evolution of at least one of the gene copies towards greater specificity of transport for selenate over sulfate [65–67]. Mutations in specific cis-regulatory sequences and changes in one or more trans-regulatory elements of the transporters may be responsible for their high and steady expression, while mutations in their coding sequence that affect protein-protein interactions and carrier function, especially in regulatory domains (e.g. STAS domain) are possible mechanisms through which selenate specificity may have evolved [64,68]. SULTR1 sequences identified in other Se hyperaccumulator species within the genus *Astragalus* (Fabaceae) for instance, possess one alanine residue in place of the glycine found in SULTR1 isoforms of non-accumulators, which may contribute to the preferential uptake of selenate over sulfate observed in these species [36].

Further indication for higher selenate specificity of sulfate transporters in *S. pinnata* than in non-hyperaccumulators is suggested by the decrease of S accumulation in *S. pinnata* supplied with increasing external selenate concentrations (high Se:S ratio) [33]. Interestingly, *SULTR1;1* for *S. pinnata* exhibited lower expression than in non-hyperaccumulators and was up-regulated by S starvation (Fig. 2), thus suggesting its minor role in selenate acquisition in this species and *SULTR1;2* as the unique root route for sulfate/selenate uptake [33]. The hypothesis that other sulfate/selenate transporters beside *SULTR1;2* may possess higher specificity for selenate over sulfate cannot be excluded and needs more investigation. One possible candidate could be *SpSULTR2;1*, which mediates the movement of sulfate into pericycle and xylem parenchyma cells for their translocation to the aerial parts of the plant and could preferentially transport selenate over sulfate [64,69,70].

2.2. Mechanisms for uptake of selenite and organic Se-compounds

Selenite is generally less bioavailable than selenate in most soils because it is strongly absorbed by iron and aluminum oxides/hydroxides, as well as by clays and organic matter [16,17]. Plants take up selenite and organic forms of Se using transport pathways that are distinct from those mediating selenate fluxes. For selenite in particular, although a passive diffusion mechanism was initially hypothesized [71–73], it is now well-accepted that its transport is largely mediated by an active mechanism that involves phosphate transporters [34,37]. Discrepancies between old and more recent studies were likely due to the effect of pH on formation of selenite species in the rhizosphere solution [74]. Indeed, at different pH values, selenite exists in varying proportions and chemical forms as H_2SeO_3, SeO_3^{2-}, and $HSeO_3^-$ [35,74,75]. Selenite in the form of H_2SeO_3 was found to be absorbed in rice via aquaporins [35] and silicon (Si) influx transporter OsNIP2;1 (Lsi1), a nodulin 26-like intrinsic membrane protein (NIP) subfamily of aquaporins [75]. In the form of $HSeO_3$, selenite enters roots sharing common transporters with phosphate [34,37]. In rice, the most abundant phosphate transporter expressed in roots, OsPT2, has been shown to possess selenite transport capacity because OsPT2-overexpressing and knockdown mutants exhibited a substantial increase or reduction in selenite uptake rates, respectively [37]. Furthermore, Se accumulation in rice grains was higher in OsPT2-overexpressing plants compared to wild-type plants. Additionally, evidence for a pivotal role of phosphate transporters in selenite uptake is provided by a number of studies that

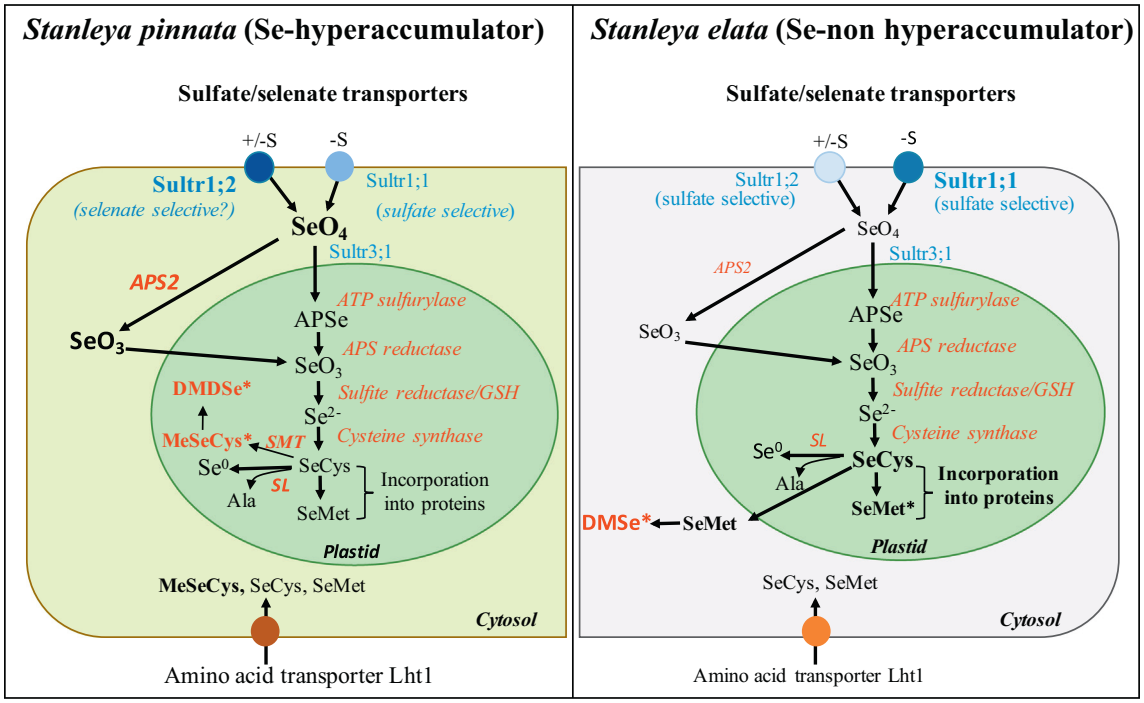

Fig. 2. Selenate/sulfate uptake and assimilation mechanisms in the model hyperaccumulator *S. pinnata* and the model nonhyperaccumulator *S. elata*. The different intensity in colour of blue circles indicates differences in expression of *Sultr1;1* and *Sultr1;2* genes between the two species in relation to S nutrition (a darker colour means higher expression). Similarly, the different intensity in colour of orange circles indicates differences in expression of the *LHT1* gene between the two species (a darker colour means higher expression). Asterisks indicate the main Se compounds accumulated in the two species. APSe, adenosine phosphoselenate; APS, adenosine phosphosulfate; GSH, reduced glutathione; SeCys, selenocysteine; SeMet, selenomethionine; SMT, selenocysteine methyltransferase; MeSeCys, methylselenocysteine; DMSe, dimethylselenide; DMDSe, dimethyl diselenide.
Adapted from Schiavon and Pilon-Smits [3].

have pointed out the decrease of selenite uptake by increases in phosphate concentration in the growth medium [35,76,77]. For instance, in perennial ryegrass (*Lolium perenne* L. cv. Evening Shade) and strawberry clover (*Trifolium fragiferrum* L. cv. O'Conner) selenite uptake dropped by about 50% when external phosphate concentration was increased 10-fold [77], and in wheat (*Triticum aestivum*) the affinity for selenite transport was reduced by the presence of phosphate [34].

Plants are also able to absorb organic forms of Se directly, primarily Se-amino acids (SeCys, SeMet and methylselenocysteine, MeSeCys) [19,78]. Studies performed with durum wheat (*Triticum turgidum*) and spring canola (*Brassica napus*) showed that SeCys and SeMet were preferentially absorbed over either selenate or selenite [78,79].

Broad specificity amino acid permeases likely play a major role in the uptake of Se amino acids, as suggested by competition studies of proline uptake in *A. thaliana* using Cys and Met as substrate competitors [80]. Interestingly, in a RNA-Seq study, an amino acid transporter was found to display significantly higher expression in Se-hyperaccumulator *S. pinnata* than in non-accumulator *S. elata* (Fig. 2), and its transcription increased in roots of hyperaccumulator by selenate [81]. It is feasible that seleno-amino acids are taken up and translocated by this amino acid transporter as well, and that this transporter contributes to Se hyperaccumulation in *S. pinnata*.

3. Se biochemistry

3.1. Plants versus organisms that require Se

As far as is known, plants do not possess essential selenoproteins, and therefore they lack systems that specifically incorporate Se-amino acids into protein structures [3,4]. Conversely, organisms that need Se are endowed with an interesting machinery that cotranslationally inserts SeCys into the active site of selenoproteins via the recoding of the opal stopcodon UGA [82,83]. SeCys in Se-requiring organisms is also referred to as the 21st protein amino acid and its use in the catalytic site of proteins offers an advantage over Cys owing to improved redox activity (5).

In selenoprotein formation, a selenocysteine insertion sequence (SECIS) in the 3′ untranslated region (UTR) of selenoproteins drives the UGA recoding as SeCys, and selenocysteine-tRNA([Ser]Sec) holds the anticodon complementary to this UGA codon [5,84]. The SeCys-tRNA initially binds the amino acid serine, which is further enzymatically converted to SeCys by modification of the hydroxyl(-OH) group to selenol (SeH) [6]. Genes containing SECIS elements are fairly similar but not identical between animals and aquatic photosynthetic organisms that need Se, and those from the microalga *C. reinhardtii* in particular, were shown to direct the synthesis of selenoproteins in mammals, thus reinforcing the hypothesis that Sec insertion mechanisms in photosynthetic organisms and animals share a common origin [1].

3.2. Se assimilation in plants: from inorganic Se to Se-amino acids

Once absorbed by plants, Se is further assimilated into Se-amino acids via the S assimilation pathway by virtue of its chemical similarity to S (Fig. 2) [3,29,18,84]. Most enzymes involved in this pathway are upregulated by S limitation in plants, but in hyperaccumulators they often show constitutive expression [4,19,64,86,87]. The assimilation process happens in part in the plastid, and the envelope-localized sulfate transporter SULTR3;1 delivers selenate from the cytosol to the stroma of the organelle [88]. The first step in selenate reduction is mediated by the enzyme ATP sulfurylase, which couples selenate (or sulfate) to ATP with formation of adenosine 5′- phosphosulfate/selenate (APS/APSe) [18,26,38,89]. This step seems to be rate limiting for Se assimilation [90]. It can take place in both the cytosol and plastids [64,91], because different isoforms of ATP sulfurylase exist in these

compartments. In *A. thaliana*, for instance, four ATP sulfurylase isoforms have been identified, three of them localizing only to the plastid (APS1, 3 and 4) and one, isoform 2 (APS2), having dual localization (cytosol and plastids) [91,92].

Interestingly, the gene encoding APS2 showed extremely elevated expression in roots of Se-hyperaccumulator *S. pinnata* compared to non-hyperaccumulator *S. elata* (over 120-fold), while in leaves its expression was 2–4 fold higher in *S. pinnata* than *S. elata* (Fig. 2) [38,81]. This observation suggests that overexpression of APS2 may be in part responsible for hypertolerance and hyperaccumulation traits in *S. pinnata*. Whether APS2 has higher specificity for selenate over sulfate is still under investigation. APS2 may be envisioned as a target for genetic engineering to develop plants with superior Se uptake, accumulation and tolerance capacity to use in both biofortification and phytoremediation technologies. Previously, only the isoform APS1 from *A. thaliana* has been overexpressed in plants [18,90]. *Brassica juncea* transgenics overexpressing APS1 exhibited increased selenate reduction and assimilation into organic Se compounds as compared to wild-type plants, which mainly contained selenate in their organs [90]. The enhanced capacity of APS-overexpressing transgenics to accumulate Se was further confirmed in greenhouse [93].

Once APSe is produced, Se assimilation proceeds towards the conversion of this compound to selenite in a rate-limiting step catalyzed by the enzyme APS reductase (APR) [18,94]. Evidence in support of a role for APR in this respect derives from studies on *A. thaliana* transgenics. *apr2-1* mutants in particular, were shown to contain high concentration of selenate and negligible amounts of selenite [95,96], as well as low S flux from sulfate to reduced S compounds and proteins [96], while plants overexpressing APR had increased Se flux throughout the plant and high rate of selenate assimilation into amino acids [18]. The catalytic capacity of APR2 was found to vary by 4 orders of magnitude across the *A. thaliana* species range and corresponds with significant differences in S and Se metabolism [96], However, among eight *Astragalus* species with varying abilities to accumulate Se, no correlation was observed between Se hyperaccumulation and APR expression [18]. Thus, APR may be more rate-limiting for Se assimilation in non-hyperaccumulators than in hyperaccumulators.

In the next step of Se assimilation, selenite is converted to selenide (Se^{2-}). This conversion has been proposed to occur enzymatically by sulfite reductase (SiR) [19,97], or non-enzymatically via glutathione-mediated reduction, with formation of selenodiglutathione (GSSeSG) and selenopersulfide (GSSeH) as intermediates, and superoxide as a byproduct [46,98]. GSSeH is then converted to selenide by the enzyme glutathione reductase (GR) [99]. Ultimately, selenide is incorporated into SeCys by the enzyme complex cysteine synthase, which catalyzes the formation of SeCys from *O*-acetylserine (OAS) and selenide [18,19,46]. The conversion of SeCys to SeMet implies the formation of the intermediates selenocystathionine and selenohomocysteine (SeHCys), and is catalyzed in series by three enzymes: cystathionine γ-synthase (CGS), which catalyzes the formation of Se-cystathionine through condensation of O-phosphohomoserine (OPH) and SeCys [18,100] and is rate-limiting for conversion of SeCys to volatile DMSe [100], cystathionine β-lyase (CBL) and methionine synthase [18,101,102]. Interestingly, several Se hyperaccumulator *Stanleya* species accumulate high concentrations of selenocystathionine in their tissues [87,103,104].

3.3. Plant mechanisms to avoid Se toxicity: hyperaccumulators versus non-accumulators

A prominent cause of Se toxicity to plants likely is the misincorporation of Se-amino acids into proteins [4,6,85]. In addition, inorganic Se anions may cause oxidative stress by depletion of the GSH cellular pool and production of the superoxide radical ($O_2^{-}\cdot$) that damages cytosolic iron-sulfur (Fe-S) clusters, mitochondrial proteins and chloroplastic iron-sulfur proteins [105]. Selenium may also be misincorporated into Fe-Se clusters, since the enzyme that releases elemental S from Cys for the formation of Fe-S clusters can also utilize SeCys as a substrate [86].

One key tolerance mechanism of Se hyperaccumulators is likely to be their capacity to prevent the incorporation of seleno-amino acids into proteins [21]. Among the different mechanisms that Se hyperaccumulators exploit, one is the methylation of SeCys to form methyl-SeCys (MeSeCys) via a reaction catalyzed by the enzyme SeCys methyltransferase (SMT) (Fig. 2) [49,106]. In this way, the amount of SeCys that non-specifically replaces Cys in proteins is significantly reduced. SMT is chloroplast-localized [107] and has been identified in both non-accumulator and Se hyperaccumulator species of the genus *Astragalus*. However, only the functional isoform of this enzyme, found in hyperaccumulators, is able to produce MeSeCys and shows preference for methylation of SeCys over Cys [106–108]. This explains why Se-hyperaccumulators, such as *A. bisulcatus* and *S. pinnata*, contain significantly high concentration of MeSeCys in their tissues than non-accumulator species, which mainly accumulate inorganic Se [18,87,104,108,109]. Although, SMT is constitutively and highly expressed in hyperaccumulators, it also can be induced by Se in some Se-accumulators (e.g. *B. oleracea*) [85,110]. SMT from *A. bisulcatus* has been overexpressed in non-hyperaccumulators *A. thaliana* and *B. juncea*, leading to enhanced Se accumulation (primarily as MeSeCys and γ-glutamyl-MeSeCys), tolerance and volatilization [111–113].

An additional mechanism by which hyperaccumulators tolerate high Se concentration in tissues is the conversion of MeSeCys into volatile dimethyldiselenide (DMDSe) (Figs. 1 and 2) [49]. This process happens in leaves, where MeSeCys is initially converted to methylselenocysteineselenideoxide (MeSeCysSeO) that is then transformed into methaneselenol (CH_3SeH) by the activity of the enzyme Cys sulfoxide lyase [114,115]. In non-hyperaccumulators, a possible metabolic shunt to mitigate Se toxicity involves volatilization of SeMet to form dimethylselenide (DMSe) [3,46,116]. The synthesis of DMSe involves first methylation of SeMet to produce Se-methyl Se-Met (SeMM) in a reaction catalyzed by the enzyme S-adenosyl-L-Met:Met-*S*-methyltransferase (MMT) [116], and then proceeds via SeMM conversion to intermediate molecule 3-dimethylselenoniopropionate (DMSeP) or directly from SeMM via the enzyme methylmethionine hydrolase [114,116,117,118]. In addition to diverting potentially toxic Se amino acids into less toxic volatile compounds, generation of Se volatile DMDSe and DMSe might also have a role in plant defense against herbivores [3,119,120].

Aside from the production of MeSeCys and volatile compounds, another metabolic route that prevent incorporation of SeCys in proteins involves the activity of the enzyme selenocysteine lyase (SL), which breaks down SeCys into elemental Se and alanine (Fig. 2) [86]. This enzyme is analogous to NifS-like Cys desulfurase proteins characterized in *A. thaliana*, whose function is to produce free S from Cys for the formation of Fe-S clusters [121]. Its overexpression in *A. thaliana* conferred higher Se tolerance and accumulation (2-fold) and decreased Se incorporation into proteins [86,113]. In the same transgenics, S accumulation was increased as well, which may explain why the formation of Fe-S clusters was not affected by higher production of elemental Se [86].

Another potentially important mechanism for Se tolerance in hyperaccumulators is the ability to sequester organic Se forms (C-Se-C compounds, likely a majority MeSeCys with minor fraction of selenocystathionine) into specific compartments away from sensitive key biochemical processes [123]. Selenium in leaves of *A. bisulcatus* was found in leaf hairs [104], and *S. pinnata* stores it in the vacuole of epidermal cells along the leaf periphery [87,104,123]. In contrast, in non-hyperaccumulator species, Se was mainly restricted in the vascular tissues [52,104]. *S. pinnata* also accumulates high concentrations of Se in the form of MeSeCys in the flowers [124].

In parallel to the assimilation of inorganic Se into non-toxic organic Se compounds and specific sequestration patterns, hyperaccumulator

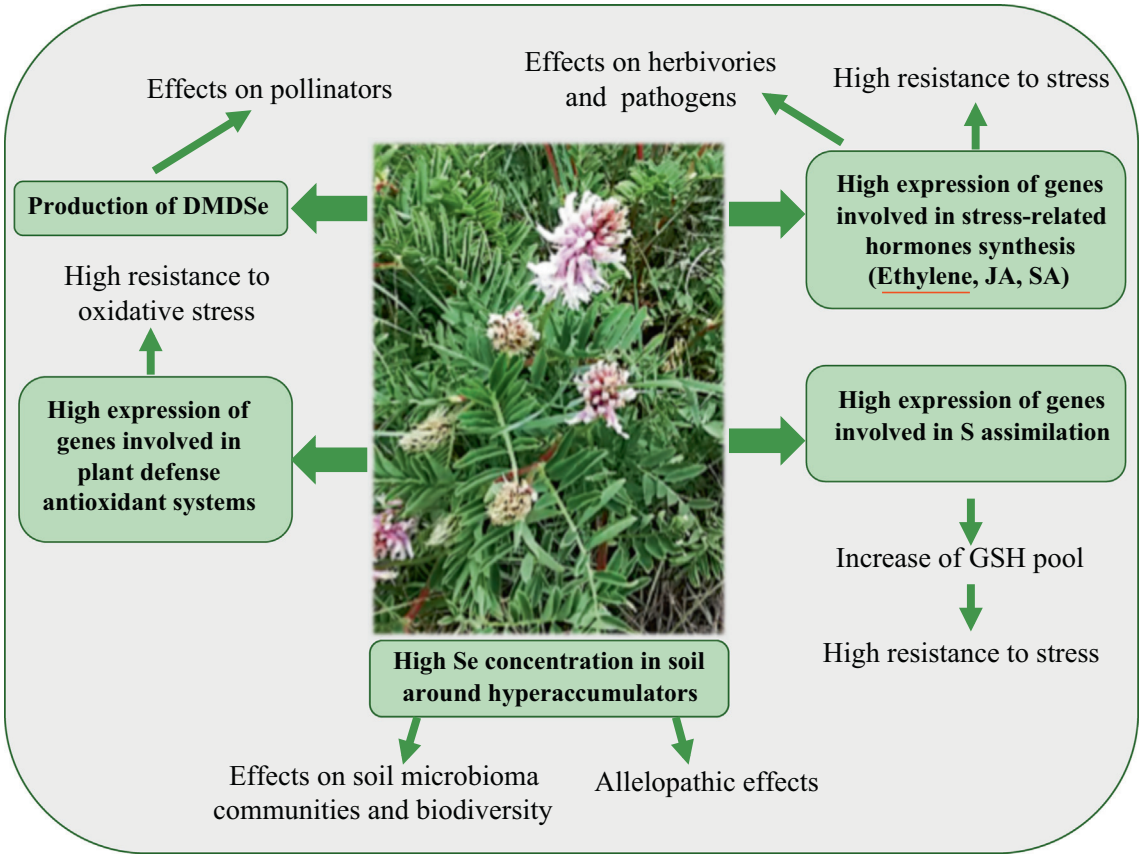

Fig. 3. Hyperaccumulator plants have constitutive high expression of defense genes and genes associates to stress-related hormones synthesis and signaling, which confers protection against herbivore and pathogen attack and protects plants from oxidative stress potentially caused by high Se concentrations in the cell. In addition to upregulation of defense networks DMDSe may have a role in protection from herbivory and influence pollination.

species appear to have constitutive upregulation of antioxidant defense systems to cope with the oxidative damage caused by the excess Se in the cellular environment (Fig. 3). While low concentrations of Se in tissues can enhance antioxidant defense mechanisms in different plant species, providing protection against abiotic stresses [26,125–128], excess Se can imbalance the cellular redox state due to the generation of reactive oxygen species (ROS) that disrupt proteins, cause peroxidation of membrane lipids and oxidative stress [11,129].

A number of studies suggest that Se is directly involved in antioxidant metabolism in hyperaccumulator plants [87,126,127]. Different defense-related enzymes and hormones are highly expressed in these plants (Fig. 3). As shown by Freeman et al. [87], hyperaccumulator *S. pinnata* has 1.5-fold higher antioxidant capacity when compared to non-hyperaccumulator *Stanleya albescens*. After 10 weeks of exposure to 20 μM selenate, the leaf concentrations of ROS $O_2^{-}\cdot$ and H_2O_2 in *S. pinnata* were lower when compared to the non-accumulator *S. albescens*. Interestingly, the total glutathione concentration in the hyperaccumulator was 1.3-fold higher than in the non-hyperaccumulator under the same conditions. Specifically, *S. pinnata* had 1.4-fold more reduced glutathione (GSH) and 1.2-fold more oxidized glutathione (GSSG) when compared to the non-hyperaccumulator *S. albescens*.

GSH, a S-containing metabolite formed from the amino acids glutamate (Glu), cysteine and glycine (Gly), constitutes a major defense mechanism against oxidative stress, participating with the ascorbate peroxidase (APX) enzyme in the ascorbate-GSH cycle [130]. The antioxidant activity in the cycle is dependent on glutathione reductase (GR), responsible for the conversion of GSSG into GSH using NADPH as an electron donor. GSH is used by the enzyme dehydroascorbate reductase (DHAR) to produce ascorbate (ASC), which is used as a substrate for the APX antioxidant enzyme activity [131]. Wang et al. [81], found that important genes mediating the synthesis of GSH (glutathione synthetase, *gsh1*), ROS scavenging (GSH peroxidase, *gpx6*, thioredoxin peroxidase, *tpx1*, ascorbate peroxidase, *apx1*) were highly expressed in *S. pinnata* as compared to non-hyperaccumulator *S. elata,* which could explain the lower ROS concentration and higher GSH content in the hyperaccumulator, suggesting that this species is more likely to deal with oxidative stress.

In addition to antioxidant enzymes, defense phytohormones such as jasmonate (JA), salicylic acid (SA) and ethylene seem to play a central role in Se tolerance and hyperaccumulation (Fig. 3) [87]. Similar processes may be important in non-accumulators. Tamaoki et al. [132] reported that enhanced Se (selenite) resistance in *A. thaliana* could be triggered by higher concentrations of jasmonate (JA) and ethylene, coupled with enhanced S uptake and reduction. Constitutive up-regulation of genes involved in signaling pathways mediated by stress hormones was also described in *S. pinnata* by Freeman et al. [87], and confirmed recently in a RNAseq study by Wang et al. [81]. Several genes implied in the biosynthesis of JA were more expressed in *S. pinnata* compared to non-hyperaccumulator *S. elata*.

While these differences between Se hyperaccumulators and non-hyperaccumulators can in part explain their different capacity to tolerate and accumulate Se, still much remains to be discovered about key genes upstream of upregulated pathways, and mechanisms for Se-specific transport. Also, a better understanding of the benefits and potential constraints of Se hyperaccumulation in high- or low-Se environments, and the interaction of Se with other defense mechanisms are fascinating questions to address further.

4. Evolutionary aspects of plant Se hyperaccumulation

4.1. Se hyperaccumulation across the plant kingdom: convergent evolution

Selenium hyperaccumulation is probably a derived trait from non-hyperaccumulators that is found in at least 45 taxa in 14 genera from 6 dicot plant families [3,19]. The trait appears to have evolved independently in different lineages, which therefore might possess distinct hyperaccumulation mechanisms. Nevertheless, hyperaccumulators from different families show many similarities in Se hyperaccumulation mechanisms, likely as a result of convergent evolution [19,133,134]. Families that include most of hyperaccumulator species are Asteraceae (genera Dieteria, Grindelia, Gutierrezia, Oonopsis, Symphyotrichum, and Xylorhiza), Amaranthaceae (genus Atriplex), Brassicaceae (genera Cardamine and Stanleya), Fabaceae (genera Acacia, Astragalus and Neptunia), Rubiaceae (*Coelospermum decipiens*) and Orobanchaceae (*Castilleja augustifolia* var. dubia) [19]. An interesting species that deserves mention because of its importance as dietary source of Se is *Bertholletia excelsa* (Brazil nut tree), which belongs to the Lecythidaceae family. *B. excelsa* is reported to accumulate up to about 68 mg Se kg^{-1} nut fresh weight, but this number can vary dramatically according to the soil in which the tree is cultivated [135].

The species and varieties within the genus *Stanleya* have been investigated for their capacity to accumulate and metabolize Se [52,123]. Tissue Se concentration differed considerably among *Stanleya* spp., with *Stanleya pinnata* var. *pinnata*, *S. pinnata* var. integrifolia and *S. bipinnata* being the unique hyperaccumulators. These all are part of the *S. pinnata* species complex, which also contains the non-hyperaccumulator *Stanleya pinnata* var. *inyoensis*. Among the taxa tested, *S. pinnata* var. *inyoensis* and *Stanleya elata* showed the lowest Se concentration, and *S. albescens*, *S. viridiflora* and *S. tomentosa* contained intermediate values. While Se hyperaccumulation appeared restricted to several members of the *S. pinnata* species complex, Se tolerance was widespread within the *Stanleya* genus [123].

4.2. Possible selection pressures driving the evolution of Se hyperaccumulation

Different hypotheses have been formulated with regard to selection pressures that may have driven the convergent evolution of Se hyperaccumulation and, more broadly, elemental hyperaccumulation in different taxonomic clades [32,134]. Selenium concentration, speciation and phytoavailability in soil may be qualifying conditions for the evolution of Se hyperaccumulation; the geographic distribution of hyperaccumulator species generally is correlated with Se distribution in soil [19]. Only a small proportion of the plant species inhabiting seleniferous soils hyperaccumulate Se, and thus the presence of Se in soil is not sufficient to explain the development of the hyperaccumulation trait, but additional physiological and ecological factors likely play a critical role. The observation that Se hyperaccumulator species mainly occur in seleniferous areas suggests that they rely on Se for their competitive fitness and perhaps their physiology [3,19]. Indeed, hyperaccumulators physiologically benefit from Se, as evidenced from a much more pronounced positive growth response to Se than non-hyperaccumulators, yet there is no evidence that they require Se [133]. However, most likely, ecological benefits from elevated Se concentrations, particularly protection from biotic stressors, are the major selective advantage of Se hyperaccumulation [32].

Mechanistically, the acquisition of Se tolerance likely evolved prior to the capacity to hyperaccumulate Se. In the genus *Stanleya*, early steps in the evolution of the Se hyperaccumulation syndrome may have enhanced Se tolerance due to higher antioxidant levels, tissue-specific Se sequestration, and high conversion of Se to non-toxic organic forms [123]. To mediate these traits, hyperaccumulators have constitutive high expression of genes involved in the synthesis of and responses to stress-related hormones (ethylene, jasmonic acid, salicylic acid), as well as enzymes involved in antioxidant processes, and in metabolic conversion of selenate to MeSeCys (Fig. 3) [81,87]. Owing to this upregulated network of abiotic and biotic defense mechanisms, hyperaccumulators have been selected in evolution to tolerate and accumulate high concentrations of Se in all their organs, with concomitant significant ecological benefits.

The ecological benefit of increased protection from herbivores and pathogens in particular, may have acted as selection pressure for the evolution from non-accumulators via Se accumulators to Se hyperaccumulators. Indeed, Se has been found to protect both Se accumulator plants like *B. juncea* and Se hyperaccumulator plants like *S. pinnata* and *A. bisulcatus* from a wide variety of herbivores and pathogens, via both deterrence and toxicity [32,120,136]. For example, in a greenhouse study leaf Se concentrations as low as 10 mg kg^{-1} DW already offered *B. juncea* protection against aphid herbivory [137] and in a 2-year manipulative field study Se concentrations up to 750 mg kg^{-1} DW were shown to protect *S. pinnata* against herbivory by black-tailed prairie dogs (*Cynomys ludovicianus*) [136]. High leaf Se concentrations were also found to protect *B. juncea* from two pathogenic fungi [137]. Interestingly, the protection by Se against herbivory seems to extend to plants growing close to hyperaccumulators [138]. Leaf damage and arthropod load was lower in *Artemisia ludoviciana* and *Symphyotrichum ericoides* individuals growing in close proximity to hyperaccumulators *S. pinnata* or *A. bisulcatus*. This was associated with higher leaf Se concentrations. In a further laboratory experiment, the protective effect of growing next to hyperaccumulators was confirmed. Grasshoppers from the same site were collected and used in choice- and non-choice feeding studies with high or low leaf Se *A. ludoviciana* and *S. ericoides* plants also collected in the field either in proximity to Se hyperaccumulator *A. bisulcatus* or away from it [138]. The grasshoppers chose to feed on the low Se plants collected away from hyperaccumulators, and suffered toxicity when forced to feed on high-Se plants collected next to hyperaccumulators [138]. The elevated Se content found in neighboring vegetation around hyperaccumulators was associated with 7–10 fold elevated soil Se concentration. Perhaps hyperaccumulators can increase their surrounding soil Se concentration via litter deposition or root exudation. While, as in the case of *A. ludoviciana* and *S. ericoides*, this may benefit neighboring plants if they are tolerant to the Se, it may mediate elemental allelopathy to Se-sensitive neighbors and thus help avoid plant-plant competition (Fig. 3) [53,133,138]. Indeed, soil collected next to hyperaccumulators was toxic to Se-sensitive *A. thaliana* [138]. Thus, hyperaccumulators can negatively or positively affect different members of the plant community nearby through the enrichment of soil with Se: the Se-sensitive neighboring species will suffer from Se toxicity, while Se-tolerant species will experience less herbivory [133,138]. Because hyperaccumulators transform inorganic to organic Se, they can change not only the concentration but also the Se speciation in the soil, which can additionally promote Se uptake by other plants (Fig. 3) [53,133].

Elevated Se concentrations in vegetation around Se hyperaccumulators may not only offer protection from herbivory, but may also promote growth. Indeed, *S. ericoides* showed a positive growth response to Se in controlled greenhouse studies [139]. As mentioned in earlier sections, low Se concentrations can promote plant growth (hormesis) via enhance photosynthesis, and induce a variety of antioxidant and defense mechanisms [125,128,140]. Selenium at low concentration in leaves has been reported to lead to decreased lipid peroxidation and to restoration of the membrane and overall structure of chloroplasts [128], via stimulation of the cellular antioxidant systems [128,141,142]. Selenium also can reduce osmotic stress via enhanced proline concentration [142,143]. Thus, low Se concentrations in plant tissues may prime plants to overcome stress conditions by upregulating plant defense systems.

4.3. Possible evolutionary constraints on plant Se hyperaccumulation

Plants maintain intimate and necessary relations with their environment through interactions with abiotic factors and mutualistic relationships with biotic partners such as pollinators and their microbiome. These interactions are important for plant physiology and reproduction. The ecological benefits of having high Se concentration in organs could be offset by ecological constraints if they impair mutualistic relationships. Therefore, understanding how Se can affect these important ecological interactions deserves special attention. In addition, it is possible that extreme Se accumulation carries a physiological burden due to toxicity.

One of the first studies analyzing the potential constraints of Se hyperaccumulation in relation to reproductive fitness was done by Quinn et al. [124]. The authors observed differences in Se speciation and allocation between the Se hyperaccumulator *S. pinnata* and non-hyperaccumulator *B. juncea*. The *S. pinnata* plants allocated Se preferentially to flowers rather than to leaves. A very specific Se distribution pattern was identified in the flowers of this hyperaccumulator, within the ovules in the pistil, and in the pollen grains, primarily as MeSeCys. In contrast, *B. juncea* showed higher Se concentration in leaves than in flowers, and different chemical forms of Se were found in the flowers, including SeCys, SeMet, MeSeCys, and the non-organic forms selenate and selenite, which could be toxic to the plant. The high Se concentration in the pollen grains of *S. pinnata* did not affect the germination rate. Conversely, high Se concentration in *B. juncea* (2200 mg Se kg^{-1}) considerably decreased pollen germination. These findings suggested that there is no physiological cost of Se hyperaccumulation for reproduction and plant fitness related to pollen germination in the hyperaccumulator. Rather, high concentrations of Se in the pollen grain might be a trait evolved for protection against herbivory in the reproductive organs of hyperaccumulators [124].

In the same study by Quinn et al. [124] no evidence was observed of any negative effects of high Se concentration in flowers of *S. pinnata* or *B. juncea* on pollinator visitation. Plants from both species with high or low Se concentrations received similar numbers of visits from the European honey bees (*Apis mellifera*) or other potential pollinators. Intriguingly, while honey bees collected from *S. pinnata* growing in seleniferous habitat contained Se concentration below 20 mg Se kg^{-1} DW, native bumble bees were found to contain more than 270 mg Se kg^{-1} DW, in the form of non-toxic MeSeCys, and were found to carry high-Se pollen in its pollen baskets. This may suggest that this native species has evolved mechanisms to tolerate the high Se concentration and may serve the ecological niche of *S. pinnata* pollinator. Somewhat similarly, Freeman et al. [104] found Se tolerant herbivores (*Plutella xylostella*) that are able to feed on *S. pinnata* and accumulate high concentrations of Se in their body, also as MeSeCys. Additionally, as mentioned above, certain Se-tolerant plant species benefit from growing close to Se hyperaccumulators. Therefore, among ecological partners of various types, there appear to be some that (co-)evolve Se tolerance so that they can have symbiotic relationships with Se hyperaccumulators.

Other mutualist symbionts that could potentially be affected by the extreme Se concentrations of hyperaccumulator plant species are rhizospheric and endophytic microorganisms. This would harm the plant, since the plant microbiome can affect the bioavailability of nutrients in the soil, influence plant growth and development and confer abiotic stress resistance [144]. A study by Sura-de Jong et al. [145], however, found no evidence of any negative effects of high Se in *S. pinnata* and *A. bisucatus* on the colonization and diversity of bacterial endophytic species. The main genera found were *Bacillus*, *Pantoea*, *Pseudomonas*, *Paenibacillus*, *Variovorax*, *Advenella*, *Arthrobacter*, and *Staphylococcus*. Similarly, in another study Alford et al. [146] found no evidence of any negative effects of Se concentration in plant tissues on the nodulation process in different *Astragalus* species (Fabaceae) in the field. Furthermore, a greenhouse experiment showed no evidence of effects of high Se in plants on nodulation index in the hyperaccumulator *A. bisulcatus* when compared to non-hyperaccumulators *A. convallarius* and *A. shortianus*. Indeed, the nodulation index increased in the hyperaccumulators (*A. praelongus* and *A. racesmosus*) with higher Se concentration in plants, which was indicative of a positive relationship between Se and the symbiotic rhizobia in these hyperaccumulator species.

Thus, while more studies are needed to investigate all the possible constraints of Se hyperaccumulation better, studies to date do not show any evidence of selection pressures constraining plant Se hyperaccumulation. Perhaps one-time constraints due to toxicity of hyperaccumulated Se have since been overcome by the evolution of Se tolerance mechanisms, in the hyperaccumulators themselves and in ecological partners [124].

5. Future prospects

There is evident progress in our understanding of plant Se metabolism, with important implications in the fields of agriculture, medicine and industry. Many research efforts to date have focused on the molecular mechanisms and ecological advantages of Se hyperaccumulation. Genes and pathways have been pinpointed that play key roles in Se tolerance and accumulation, which opens the way for future research aiming at the generation of plants with enhanced potential to accumulate and tolerate Se. These plants could be used both to deliver dietary Se to populations living in low-Se areas (biofortification) and to remediate soil and water contaminated with excess Se (phytoremediation). In addition to genes that are directly involved in selenate/sulfate transport and assimilation and antioxidant functions, others could be investigated that may be involved more upstream in triggering the Se hyperaccumulation “syndrome”. Specifically, receptors involved in triggering ethylene, jasmonic acid and salicylic acid-mediated responses could be investigated in relation to Se metabolism. One or more “master switches” may control the complex network of defense signaling pathways in plants, acting as activators of defense-related hormones, which in turn upregulate Se/S acquisition mechanisms in plants, together with antioxidant responses. Such genes likely not only influence Se metabolism but also influence the plant's relationship with ecological partners and responses to abiotic stress. Other questions that may be addressed are: do Se hyperaccumulators have selenate-specific transporters? Why do Se hyperaccumulators show such a strong positive growth response to Se, relative to other species? Could S-unrelated Se metabolic pathways exist in hyperaccumulators? How does Se interact with other metabolites in plants, such as other defense compounds? How important is Se (hyper)accumulation for plant fitness in seleniferous habitats, and which possible constraints does it carry in seleniferous and non-seleniferous habitats?

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