Disentangling the complexity and diversity of crosstalk between sulfur and other mineral nutrients in cultivated plants

Highlights: Sulfur deficiency modifies in a characteristic manner the plant ionomic signature leading to numerous crosstalks with at least five macronutrients (N, Mg, P, K and Ca) and eight micro or beneficial nutrients (B, Cl, Mn, Fe, Cu, Mo, Na and Se).

Abstract
A complete understanding of ionome homeostasis requires a thorough investigation of the dynamics of the nutrient networks in plants. This review focuses on the complexity of interactions occurring between S and other nutrients, and these are addressed at the level of the whole plant, the individual tissues, and the cellular compartments. With regards to macronutrients, S deficiency mainly acts by reducing plant growth, which in turn restricts the root uptake of, for example, N, K, and Mg. Conversely, deficiencies in N, K, or Mg reduce uptake of S. TOR (target of rapamycin) protein kinase, whose involvement in the co-regulation of C/N and S metabolism has recently been unravelled, provides a clue to understanding the links between S and plant growth. In legumes, the original crosstalk between N and S can be found at the level of nodules, which show high requirements for S, and hence specifically express a number of sulfate transporters. With regards to micronutrients, except for Fe, their uptake can be increased under S deficiency through various mechanisms. One of these results from the broad specificity of root sulfate transporters that are up-regulated during S deficiency, which can also take up some molybdate and selenate. A second mechanism is linked to the large accumulation of sulfate in the leaf vacuoles, with its reduced osmotic contribution under S deficiency being compensated for by an increase in Cl uptake and accumulation. A third group of broader mechanisms that can explain at least some of the interactions between S and micronutrients concerns metabolic networks where several nutrients are essential, such as the synthesis of the Mo co-factor needed by some essential enzymes, which requires S, Fe, Zn and Cu for its synthesis, and the synthesis and regulation of Fe-S clusters. Finally, we briefly review recent developments in the modelling of S responses in crops (allocation amongst plant parts and distribution of mineral versus organic forms) in order to provide perspectives on prediction-based approaches that take into account the interactions with other minerals such as N.
Chlorine, copper, ionome, ionomic signature, iron, molybdenum, selenium, sulfur
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Introduction
Ionomic composition in plants: the result of multiple regulation and interactions
The concept of the ionome in living organisms emerged more than a decade ago, resulting from the availability of relatively high-throughput and low-cost analytical systems, and Salt et al. (2008) defined it as ‘the mineral nutrient and trace element composition of an organism, and represents the inorganic component of cellular and organismal systems’. More recently, White et al. (2017) have considered the functional ionome, which includes all mineral elements whether they be essential or non-essential for life, and these can be classified into the macronutrients nitrogen, phosphorus, potassium, calcium, magnesium, and sulfur, and into the micronutrients chlorine, boron, iron, manganese, copper, zinc, nickel, and molybdenum (White and Brown, 2010). However, other studies have indicated that additional elements from the periodic table may also be required, but their essentiality for optimal plant growth and development is still under discussion; these include selenium (White et al., 2004; Van Hoewyk et al., 2008), silicon (Epstein, 1999), and vanadium (Welch and Huffman, 1973). Furthermore, plant tissues contain numerous

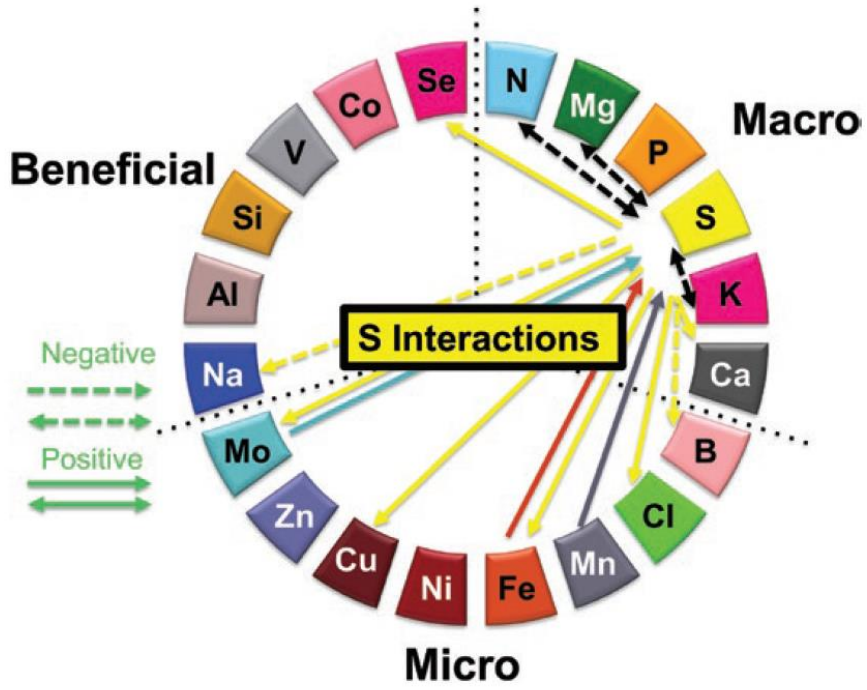
other trace elements that may affect plant metabolism, such as non-essential heavy metals, or that result from plant exposure to the soil and atmospheric environment. These elements could be considered as being constitutive in the environmental ionome and may be used to detect anthropogenic pollution (e.g. As, Cd, Hg, Pb) or to fingerprint geographical origins of agricultural products, such as Sr and Rb in the grains of rice (Oryza sativa) (Cheajesadagul et al., 2013) or Cr, Ga, Rb, Sr, and Zr in wheat (Triticum aestivum) (Zhao et al., 2013).

It is widely acknowledged that plant mineral composition is tightly regulated at the uptake, binding, translocation, storage or sequestration, and remobilisation levels, amongst other mechanisms. This ensures that plant requirements for growth are met whilst the toxicity that results from excessive accumulation is avoided. The complexity of such homeostatic regulation has been at least partly characterised (see for example the review on targeting trace metals by Andresen et al., 2018). Nevertheless, the multiple interactions between nutrients have been discovered in a piecemeal way, suggesting the need for more global approaches to studying plant mineral nutrition as a whole. Although by no means exhaustive, the diagram of the ionomic network presented by Baxter (2009) was one of the first illustrations in the plant kingdom of the multiple interactions and crosstalk of a specific ionome. It clearly showed that the multiple levels of interactions that generate plant ionomic composition can be the result of the chemical analogy or similarities between elements, the genetic background, the environmental conditions, and the interactions of these factors. The consequences of chemical analogy or partial similarity can be observed for elements and their derived ions at the transporter level. For example, the uptake of chemical analogues of K (Rb), Ca (Sr), and S (Se) have frequently been used as a proxy to characterise the uptake of these macro-elements. In a similar way, it has been shown that the interaction between As and P results from a potential transport of arsenate by phosphate transporters. An additional example can be seen in transporters that show broad specificity, such as IRT1 (Iron Regulated Transporter 1) that can take up Fe as well as Mn, Co, Zn, and Cd. At the genetic level, ionomic screening of large collections of mutagenised populations of Arabidopsis revealed groups of elements that were positively correlated, such as As, Fe, Na, Zn, and Mo, Mg and Ni or Mn, and Ca and Sr (Lahner et al., 2003). An example of how a simple physiological trait can have wide-ranging effects on the plant ionome is shown by the chararcterisation of one of the mutants identified in the study of Baxter (2009). Accumulation of suberin (probably in the Casparian strip) reduces permeability and leads to decreased transpiration, and this is associated with decreases in leaf contents of Ca, Mn, and Zn, but also with increases in S, K, and Mo. It was suggested that this global effect was a result of the pathway used by elements to enter the xylem (via symplastic or apoplastic pathways). Ionomic analyses performed by Baxter et al. (2008) in Arabidopsis under variable environments indicated that Fe deficiency significantly increased Mn, Co, Zn, and Cd leaf contents and this was also the case for B, Zn, and As under P deficiency. Analyses of genetic diversity between different plant species grown under various environments have revealed some close correlations between Ca and Mg (Watanabe et al., 2007; Baxter et al. (2008). In recent years numerous breakthroughs have occurred, mostly combining ionomic analysis with systematic screens of mutants or with analysis of natural genetic variation. While out of the scope of this review, some of this work has been detailed in recent papers (Barberon et al., 2016; Huang and Salt, 2016) and has included the identification of genes involved in ionome constitution and regulation, the deciphering of Casparian strip synthesis and regulation as well as its role in the leaf ionome, and the identification of environmental adaptations to saline or acidic soils that involve specific transporters.

Some impressive results have been provided by genome-wide analysis of the ionome. In Arabidospsis, an inductively coupled plasma mass-spectrometry analysis of thousands of plants revealed that of those with different ionome compositions, just 11% differed in only one element (Lahner et al., 2003). Two other milestone studies were conducted on Saccharomyces cerevisiae. In the first, Eide et al. (2005) used 4385 strains and showed that ionomic profiles were modified in 212 of them, of which, surprisingly, only four were affected for one element alone. In the second study, Yu et al. (2012) used nearly 12 000 strains (haploid, diploid deletion strains, and overexpression strains), of which nearly 9% showed an altered ionome, allowing the identification of 584 genes that could be involved in the regulation of the yeast ionome under optimal nutrient supply. These early studies, which were mostly limited to model organisms, showed that the ionomic composition of plant tissues is coordinately regulated, reflecting plant mineral status (Baxter et al., 2008), and that plant mineral composition should be evaluated as a whole (Baxter, 2015; Pii et al., 2015).

The functional ionome of plants is modified by S availability

Numerous studies have considered the effects of S deficiency in plants at the metabolic or transcriptomic levels, for example, in Arabidopsis (Hirai et al., 2003; Forieri et al., 2017), in Triticum durum (Ciaffi et al., 2013), and in Medicago truncatula (Wipf et al., 2014); however, to the best of our knowledge, very few studies have considered the consequences of S deficiency on the composition of the leaf functional ionome evaluated as a whole (exceptions being Maillard et al. 2015, 2016a, mostly in Brassica napus). As a consequence, partial data obtained from papers evaluating the effects of S deficiency on selected nutrient concentrations in different species have been used to broaden the conclusions obtained in B. napus. When focusing on the functional ionome of plants subjected to different levels of S availability, several negative and positive interactions between sulfur and other nutrients have often been reported, as illustrated in Fig. 1, which has been compiled from different studies. Amongst them, S deficiency reduces the uptake of N, Mg, and K, and vice versa. The best described effect concerns the negative impact of S shortage on N metabolism as a whole, including on uptake and assimilation, and consequently on the growth, yield, and quality of harvested products in most cultivated species, such as forage crops (Tallec et al., 2008; Varin et al., 2010), peas (Pisum sativum) (Zhao et al., 1999), oilseed rape (B. napus) (McGrath and Zhao, 1996; Abdallah et al., 2010; Sorin et al., 2015), and wheat (Shinmachi et al., 2010) amongst others. A more specific effect of S has also been shown on N2 fixation in legumes (Tallec et al., 2009; Varin et al., 2010) in relation to specific sulfate transporters that are expressed in nodules and are essential for N2 fixation (Krussell et al., 2005). The contents of some leaf micronutrients such as Na and B are also lowered by S deprivation, but to our knowledge very little information is available on the causal relationships. More surprisingly, suboptimal S nutrition may increase the leaf concentrations of other nutrients. Se and Mo, and specifically their anionic forms, SeO_4^{2-} (White et al., 2004) and MoO_4^{2-} (Shinmachi et al. 2010), are taken up by roots at a greater rate, probably as a result of their similarity to sulfate and hence due to the involvement of sulfate transporters that are up-regulated under S limitation (Maillard et al. 2016b). The case of Mo is unique but is similar to Mn and Fe, as their deficiency also leads to an increase in sulfate uptake. The leaf concentrations of two other micronutrients, Cl (Sorin et al., 2015; Etienne et al., 2018) and Cu (Maillard et al., 2016b), are also increased during S starvation. Fig. 1.



Interactions between S and other elements of the functional ionome of Brassica napus subjected to individual mineral deficiency. Interactions resulting from S deficiency (indicated by the lines) lead to reduced or increased uptake of other nutrients (dashed and solid lines, respectively). Deficiencies in Fe, Mo, or Mn lead to increased S uptake.

Redrawn from Maillard et al. (2016a).
Fig. 1.

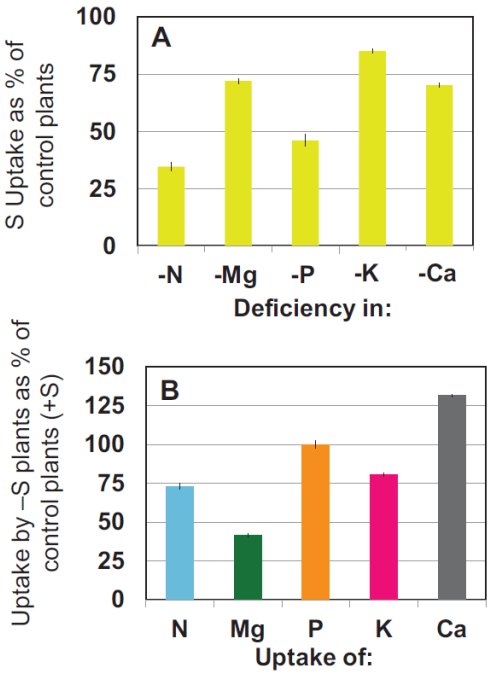
Overall, the change in the ionomic signature resulting from different S availabilities suggests that numerous crosstalk mechanisms are involved. Therefore, with a focus on cultivated species, this paper aims to review the current literature in order to identify the mechanisms involved in generating the specific ionomic signatures that result from different S availabilities. The consequences of deficiency in terms of yield and quality of harvested products will be described, gaps in our knowledge will be highlighted, and potential applications for filling those gaps—such as modelling and nutritional indicators—will be considered.

Crosstalk between S and other macronutrients

Non-legume species

Interactions between S and other macronutrients have been described for numerous species; however, most studies have tended to focus on N, P, and K. A global overview can be proposed from data published by Maillard et al. (2016a) (Fig. 2). Historically, all these interactions have been described under Liebig's law of the minimum (first proposed by Justus von Liebig in 1840; see Salisbury, 1992), which states that growth is driven by the most limiting factor; reduced growth in turn down-regulates the root uptake of other nutrients. In B. napus, root S uptake is reduced by a spectrum of nutrient deficiencies, but mostly by low levels of N (–75%), P (–54%), Ca (–30%), Mg (–28%), and K (–15%) (Fig. 2A). On the other hand, S deficiency mostly reduces the root uptake of Mg (–48%), N (–27%), and K (–20%) (Fig. 2B). More surprisingly, uptake of P and Ca under S deficiency is either unaffected or slightly increased, respectively, and it has been proposed that S and P metabolism could be co-regulated (Briat et al., 2014). Indeed, Phosphate Starvation Response 1 (PHR1), a MYB-like transcription factor initially implicated in P homeostasis, has been shown to be an important link between P and other macronutrients such as S (Rouached et al., 2011), but also N (Maeda et al., 2018), Zn (Khan et al., 2014), and Fe (Bournier et al., 2013). For

example, it has been shown that PHR1 positively regulates SULTR1.3 expression and inhibits SULTR2.1 (Rouached et al., 2011).
Fig. 2.



Interactions between macronutrients in Brassica napus. (A) Root S uptake expressed as a percentage of the values in controls in plants subjected to N, Mg, P, K, or Ca deficiency. (B) Effects of S deficiency on root uptake of N, Mg, P, K, and Ca expressed as a percentage of the control plant values. Data are means (±SE), fr n=16. Redrawn from Maillard et al. (2016b).

One of the best described regulatory pathways concerns TOR protein kinase, which is involved in the coordination of C and N metabolism together with the regulation of meristem activity (Dobrenel et al., 2016). Its involvement in S sensing has also recently been demonstrated. Cysteine, which is a key compound for S metabolism, is an interesting candidate to coordinate the availabilities of N, C, and S with growth. Dong et al. (2017) demonstrated that cysteine is not sensed by itself but rather via its biosynthetic precursors, O-acetylserine (OAS) and sulfide. Indeed, cysteine synthesis depends on the OAS C/N backbone, which is controlled by the activity of serine acetyltransferase (SERAT), and on the provision of sulfide via the activity of sulfite reductase (SiR). By comparing Arabidopsis plants knocked-out for either the SiR gene or the three SERAT genes, Dong et al. (2017) demonstrated that availability of the C/N backbone is sensed by GCN2 kinase, and that S limitation leads to a decrease in TOR kinase activity concomitant with a decrease in glucose and sucrose concentrations. Thus, working together, these two kinases allow plants to distinguish between C/N and S limitations and to coordinate C, N, and S fluxes for adequate sulfur assimilation and control of plant growth (Dong et al., 2017). Recently, it has been shown in S. cerevisiae that TOR complex1 (TORC1) is involved in the response and regulation of potassium fluxes (Primo et al., 2017), which may suggest that TORC1 could be involved in the regulation of other nutrient homeostasis in higher plants.

Specific interactions between S availability and N2 fixation in legumes

General effects

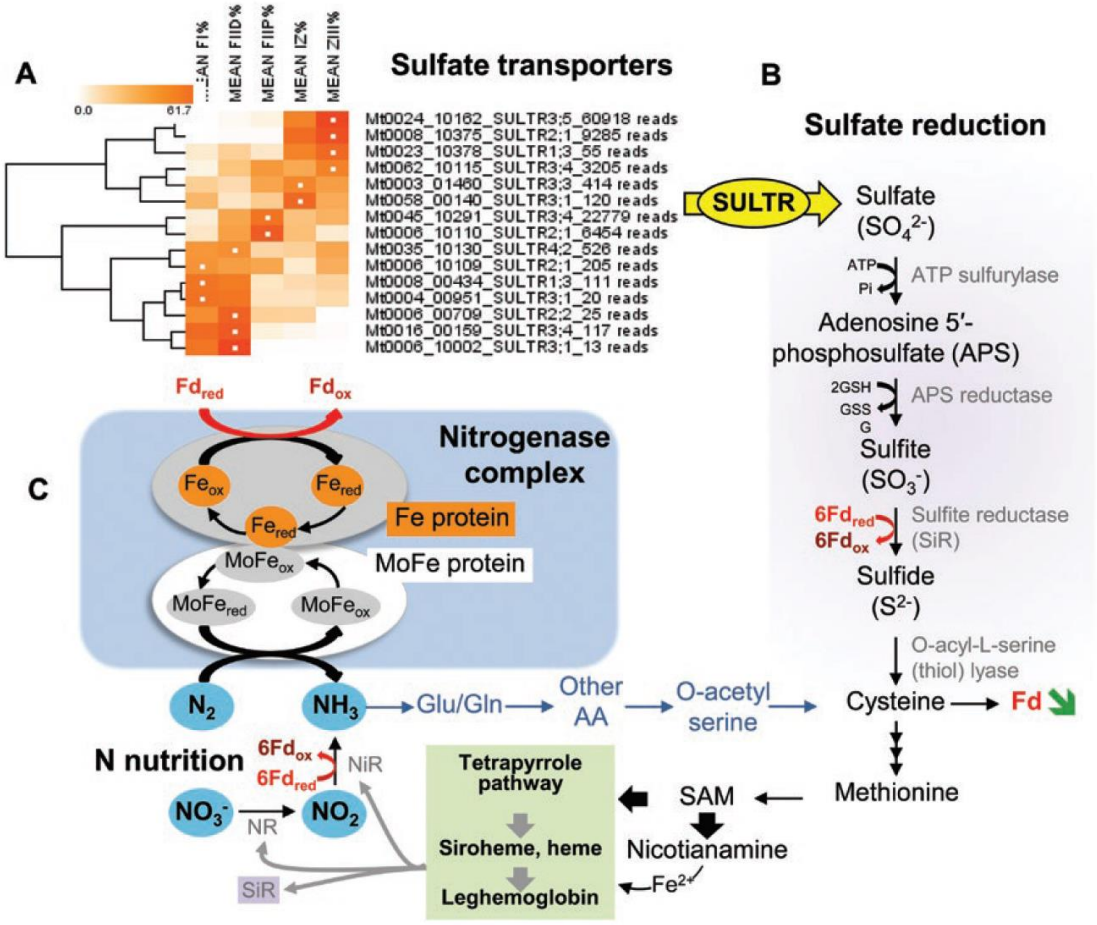
Total nodule biomass, and nodule size and number have been shown to be positively correlated with S-nutrition in some legume species (Anderson and Spencer, 1950), and this results from greater root growth and nodule density per unit root length (Gilbert and Robson, 1984, Scherer and Lange, 1996). As such, nodule number per se does not limit N2 fixation, and the mechanisms by which it is affected by S deficiency may be due to a feedback system mediated by accumulation of free amino acids (Janssen and Vitosh, 1974), similar to the mechanism suggested for inhibition of N2 fixation via free amino acids (Parsons et al., 1993; Bacanamwo and Harper, 1997; Neo and Layzell, 1997).

Nodules contain high S concentrations that probably reflect their high S requirement for functioning (Zhao et al., 1999). For example, it has been shown that nodules from white clover can contain up to 3% S per unit DW, which is about a 6-fold greater concentration that in the leaf (Varin et al., 2010). Such high requirements for S in nodules probably reflect the need for S in the synthesis of specific compounds required for N2 fixation, such as leghemoglobin, nitrogenase, Fe-S clusters, and ferredoxin (Fd). Dinitrogen fixation relies on the soluble electron-carrier protein Fd and the ammonium-reducing nitrogenase (Nase), key enzymes that contain Fe-S-clusters (Mortenson and Thornley, 1979; Yoch, 1979; Marschner, 1995). Nase is highly enriched in S-amino acids and large amounts of sulfur are necessary to ensure full enzyme activity, which relies on S-rich proteins including dinitrogenase and NifH protein (Thiel and Pratte, 2014; Zhang et al., 2015). Nase activity is more negatively affected than photosynthesis under S-deficient conditions, with S deficiency reducing N2 fixation due to deactivation of Nase (Scherer and Lange, 1996; Pacyna et al., 2006; Scherer et al., 2008; Khan and Mazid, 2011). In Lotus japonicus, S deficiency reduces NifH protein concentration and this leads to decreases in Nase complex activity (Krusell et al., 2005). For its functioning, Nase requires ATP plus adequate supplies of carbohydrates and reducing equivalents derived from efficient electron transfer via Fd. S deficiency has been reported to lower ATP energy levels in both bacteroids and host cell mitochondria, and to lower the Fd concentration in bacteroids (Scherrer et al., 2008; Varin et al., 2010). Leghemoglobin content, which determines the O2 supply to Nase, is also reduced by S deficiency (Scherer et al., 2008).

Specific S transport is required for N2 fixation

It has been reported that specific mechanisms may be required to increase sulfate allocation to nodules, and this has been partly characterised in model species. In M. truncatula, the different zones of the nodules have been analysed by transcriptomics based on RNA-sequencing after laser-capture microdissection (Roux et al., 2014). By retrieving the list of genes annotated as sulfate transporters (15 identifiers), we were able to explore their sites of expression within nodules (Fig. 3A). Interestingly, four sulfate transporter (SULTR) genes are preferentially expressed in the zone furthest from the apical meristem (zone III), where nitrogen fixation by bacterial nitrogenase occurs. This suggests the presence of active sulfate transport systems in this zone. One of these, annotated as SULTR3;5 by homology with Arabidopsis, shares 75% identity with SST1, the Symbiotic Sulfate Transporter 1 of L. japonicus whose loss of function abolishes nitrogen fixation, leading to growth defects under symbiotic conditions (Krusell et al., 2005). In the expression tree, SULTR3;5/SST1 is clustered with a sulfate transporter of group 2, SULTR2;1, implying that both genes could cooperate in nodules, as previously shown in Arabidopsis roots (Kataoka et al., 2004). The two additional sulfate transporter genes, homologous to SULTR1;3 and SULTR3;4, displayed

maximum expression levels in zone III, thus highlighting the importance and complexity of sulfate transport systems in the nitrogen-fixing zone.
Fig. 3.



Interactions between S metabolism and N2 fixation in legume nodules. (A) Expression patterns of sulfate transporter genes in the nodule zones. The data are from Roux et al., (2014) and were obtained by RNA sequencing of the apical meristem zone (FI), distal fraction (FIID), proximal fraction II (FIIP), interzone (IZ), and zone III (ZIII). The colour coding indicates the relative read distribution among zones (%) for the sulfate transporter genes displaying a minimum of 10 total reads (dots indicate maximum values). The annotation corresponds to the name of the closest Arabidopsis homologue. (B) Sulfate reduction pathways leading to the synthesis of cysteine and methionine. (C) Nitrogen nutrition modes based on nitrate acquisition or atmospheric nitrogen fixation and interactions with S metabolism. The green arrow indicates a reduced abundance in nodules of plants grown under S-limiting conditions (Scherer et al., 2008). Fd, ferredoxin; NR, nitrate reductase, NiR, ferredoxin nitrite reductase.
Fig. 3.

Sulfate in the nodules is converted into adenosine 5´-phosphosulfate by ATP sulfurylase (APS), then into sulfite by APS reductase, and finally into sulfide in a reaction catalysed by sulfite reductase (Kalloniati et al., 2015). Sulfide in the nodules can support cysteine synthesis, which

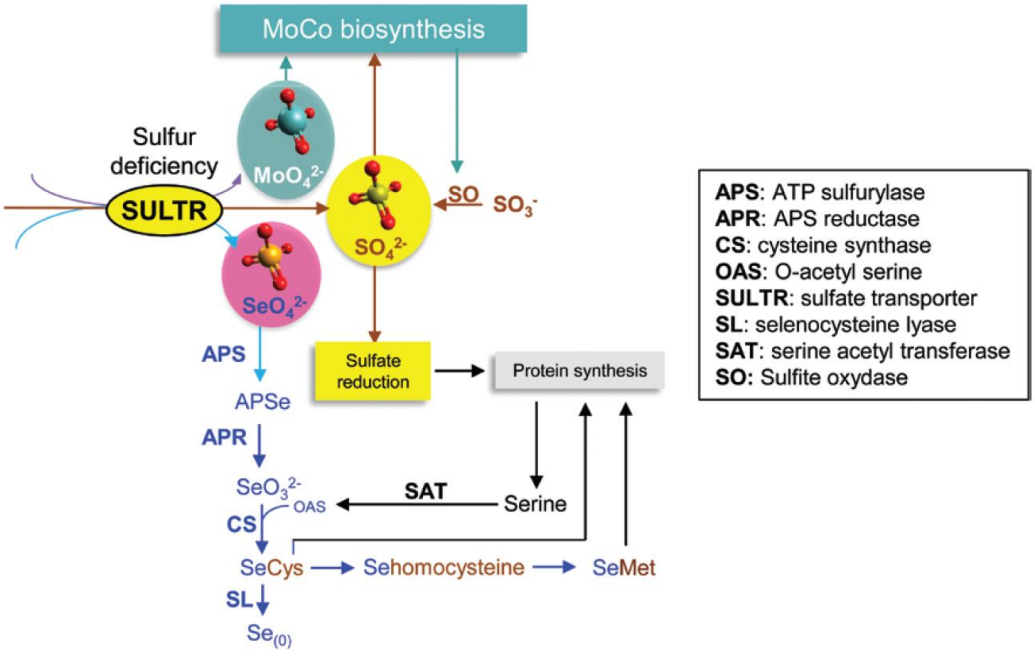
occurs in combination with OAS derived from nitrogen assimilation (Fig. 3B). This reaction, catalysed by OAS (thiol) lyase, is a merging point in the S and N assimilation pathways in different plant tissues, including nodules (Kalloniati et al., 2015). Moreover, studies in Arabidopsis and barley have shown that OAS acts as a positive effector of the expression of genes encoding sulfate transporters and enzymes of S assimilation, such as sulfite reductase (Smith et al., 1997; Koprivova et al., 2000). Owing to the strong transcriptional changes in the S assimilation pathways within nodules of L. japonicus (Kalloniati et al., 2015), it is plausible that such positive feedback activation by O-acetylserine also occurs in the nitrogen-fixing zone. Cysteine is a precursor of S compounds that play key roles in nodules such as Fd, which acts as an electron donor for sulfite reductase, nitrite reductase, and nitrogenase activities (Fig. 3C). Moreover, a gene encoding a Fd-dependent nitrite reductase (Medtr4g086020) is preferentially expressed in the nitrogen-fixing zone of M. truncatula roots (zone III in Roux et al., 2014), suggesting that nitrite can be converted into ammonia in a Fd-dependent manner in this zone. This would limit the accumulation of nitrite, which is well known for its inhibitory effect on nitrogenase activity (Trinchant and Rigaud, 1982). In an a priori approach to investigate whether S-dependent processes might be preferentially active in the nitrogen-fixing region of the nodules, we performed a gene enrichment analysis from the list of M. truncatula genes preferentially expressed in zone III (data extracted from Roux et al., 2014). This revealed two main gene ontology (GO) terms that were over-represented ($P<0.05$), namely ‘anion transport processes’ (GO:0008509) and ‘oxidoreductase activity’ (GO:0016627). Consistent with a key role of sulfate transport in the nitrogen fixing zone, ‘anion transport processes’ contains six genes of which three correspond to the sulfate transporter genes at the top of the cluster in Fig. 3A. The term ‘oxidoreductase activity’ also contains six genes, of which two are related to the tetrapyrrole biosynthetic pathway. This pathway leads to the synthesis of heme and siroheme, which are prosthetic groups central to the activity of nitrate reductase and nitrite/sulfite reductase, respectively (Tripathy et al., 2010). The first gene (Medtr7g034345) encodes uroporphyrinogen III methyltransferase, which synthesises siroheme from uroporphyrinogen. This methyltransferase uses S-adenosylmethionine (SAM), an end-product of S metabolism, as a methyl donor. The second gene encodes coproporphyrinogen III oxidase, involved in the synthesis of heme, which is the precursor of leghemoglobin. A characterisation of coproporphyrinogen III oxidase from Escherichia coli revealed that this enzyme needs to consume two molecules of AdoMet to be active (Layer et al., 2005). SAM is also utilised in the synthesis of nicotianamine, which may supply the bacteroid with Fe, an essential micronutrient required for nitrogenase activity and leghemoglobin synthesis (Hakoyama et al., 2009; Avenhaus et al., 2015). These data highlight that part of the sulfate transported in the nodules may be used for the synthesis of SAM, which might help to control nitrogen fixation in nodules. The sulfate transporters SULTR3;5, SULTR2;1, and SULTR1;3 (Fig. 3A) are key candidates to release sulfate in the nitrogen-fixing zone for regulating these S-dependent metabolic activities.

Crosstalk between S and micronutrients

Root uptake of sulfate, molybdate, and selenate

Following the study of White et al. (2004) with Arabidopsis, the experiment conducted by Shinmachi et al. (2010) is probably unique in the sense that the expression of sulfate transporters in T. aestivum was studied in field conditions under different S fertilisation regimes, together with the accumulation of S, Se, and Mo in different tissues. Lack of S fertilisation led to greater expression of Sultr1.1 (a plasmalemmal sulfate transporter) in all tissues, and this was proposed as a reason for the increased accumulation of Mo and Se compared to plants fertilised with S. This in

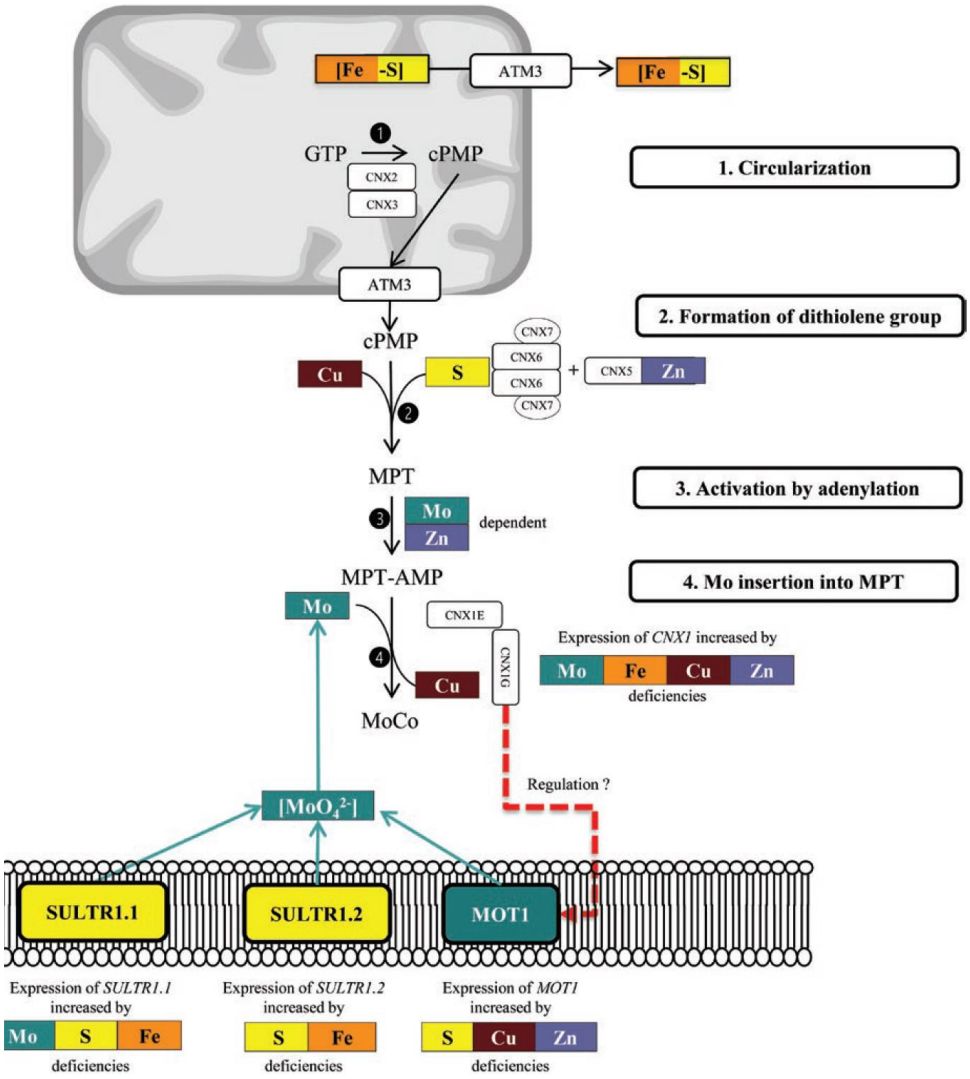
turn points towards SO42–, MoO42–, and SeO42– competing for the same transporters and explains the antagonistic effects of S, Mo, and Se fertilisation that have reported (Li et al., 2008; Schiavon et al., 2012). In the meantime, Sultr4.1, a tonoplastic transporter that is assumed to be involved in the efflux of sulfate from the vacuole, was also up-regulated, which coincided with a decrease in S (mostly from sulfate) and Se from the leaves and their respective increase in the grains. A lower remobilisation of Mo to the grains was noted, suggesting a lack of transport of MoO42– by SULTR4.1. On the other hand, the expression of Sultr5.2 (later renamed as Mot1.1 because it is thought to be involved in Mo accumulation) in wheat roots is not affected by S supply and therefore it cannot fully explain the patterns of Mo accumulation (Shinmachi et al., 2010). Maillard et al. (2016b) found the same increased uptake of Mo in B. napus, which preceded the drop in leaf S content under S deprivation, and it coincided with a strong and fast up-regulation of Sultr1.1 and Sultr1.2. The same pattern of Mo accumulation was also found following cessation of the S supply in different cultivated species including T. aestivum, Zea mays, P. sativum and Solanum lycopersicum. However, Arabidopsis mutants examined for activity of either of these two genes retained this increase in Mo uptake, implying the involvement of other transporters that were probably up-regulated by S deprivation. This demonstrated that the ratio of Mo/S in leaves of cultivated plants could potentially be used as a proxy to evaluate S nutrition and hence to enable adjustment of the levels of S fertilisation (Maillard et al., 2016b).
Se, commonly classified as a beneficial element for plant growth, shows chemical similarities to S. Indeed, SeO42– is predicted to be taken up by root plasma membrane sulfate transporters (Fig. 4; Gupta and Gupta, 2017). Following assimilation, Se is converted to selenite, and combined with OAS by cysteine synthase to form selenoamino acids, selenocysteine (SeCys), and selenomethionine (SeMet) (White, 2016). SeCys and SeMet can be integrated into proteins to synthesise seleniated proteins.
Fig. 4.



Potential sulfate, molybdate, and selenate uptake by SULTR root transporters and assimilation of Se into amino-acids and proteins. Adapted from White (2016) and Gupta and Gupta (2017).

Fig. 4.

The synthesis of the Mo co-factor may explain some of the crosstalk between S, Cu, Fe, Zn, and B. As already noted, S deficiency strongly increases Mo uptake and coincides with the up-regulation of the expression of the plasmalemmal sulfate transporters SULTR1.1 and SULTR1.2 (Shinmachi et al., 2010; Maillard et al., 2016b). Mo, which is a transition metal, is absorbed as molybdate and then needs to be complexed by a Mo-binding pterin to form a functional Mo co-factor (Moco). Moco is considered to be crucial for all organisms, and is inserted into different molybdo-enzymes in plants. These include nitrate reductase and nitrogenase, which have a crucial role in N metabolism; xanthine dehydrogenase, which participates in the catabolism of purine; sulfite oxidase, which is involved in stress tolerance against sulfur dioxide; and aldehyde oxidase, which is needed in the synthesis pathway of abscisic acid (Bittner, 2014). In addition, a fifth group of Mo-dependent enzymes probably exists in the plant genome (Ott et al., 2015). One of these enzymes, namely mitochondrial amidoxime reducing component (mARC), is responsible for the reduction of N-hydroxylated substrates (Bittner, 2014). Moco synthesis starts in mitochondria (Fig. 5) and requires transient protein–protein interactions that act as a protection mechanism during transport of the highly oxygen-sensitive Moco (Kaufholdt et al., 2017). At four different steps of Moco synthesis, Cu, Fe, S, and Zn are also required (Fig. 5). While Mo uptake is strongly increased under S deficiency, it also increases under Mg, Fe, Zn, Mn, Cu, or B deficiency, but to a smaller extent (Billard et al., 2014; Maillard et al., 2016a; Vigani et al., 2017). This could be a least partly explained by an increased expression of Sultr1.1 and Sultr1.2 under Fe, Mn, or B deficiency, while expression of MOT1, which is one of the first plasmalemmal molybdate transporters, is up-regulated by S, Cu, or Zn deficiency (Fig. 5; Maillard et al., 2016a). Overall, this provides evidence that the biosynthesis network of Moco and its regulation account for at least some of the crosstalk between S and Cu and Zn (Fig. 1) as deficiencies of any of these will reduce Moco synthesis, leading to an up-regulation of root sulfate and/or molybdate transporters. Interactions between Mo and Fe during Moco synthesis were suggested by Bittner (2014) and have been observed in cucumber (Vigani et al., 2017). In Fe-deficient cucumber plants, increased cPMP and Moco contents have both been observed, indicating that there is an impact of low Fe on Mo homeostasis as early as the first step in Moco biosynthesis (Vigani et al., 2017). B is mostly involved in the synthesis of rhamnogalacturonan II, which is present in primary cell walls as a component of highly complex pectic polysaccharides (Funakawa and Miwa, 2015), but how B and S are connected remains more difficult to explain because deficiency of B increases the expression of Sultr1.1 and Sultr1.2, whereas S deficiency decreases B uptake (Maillard et al., 2016a).
Fig. 5.

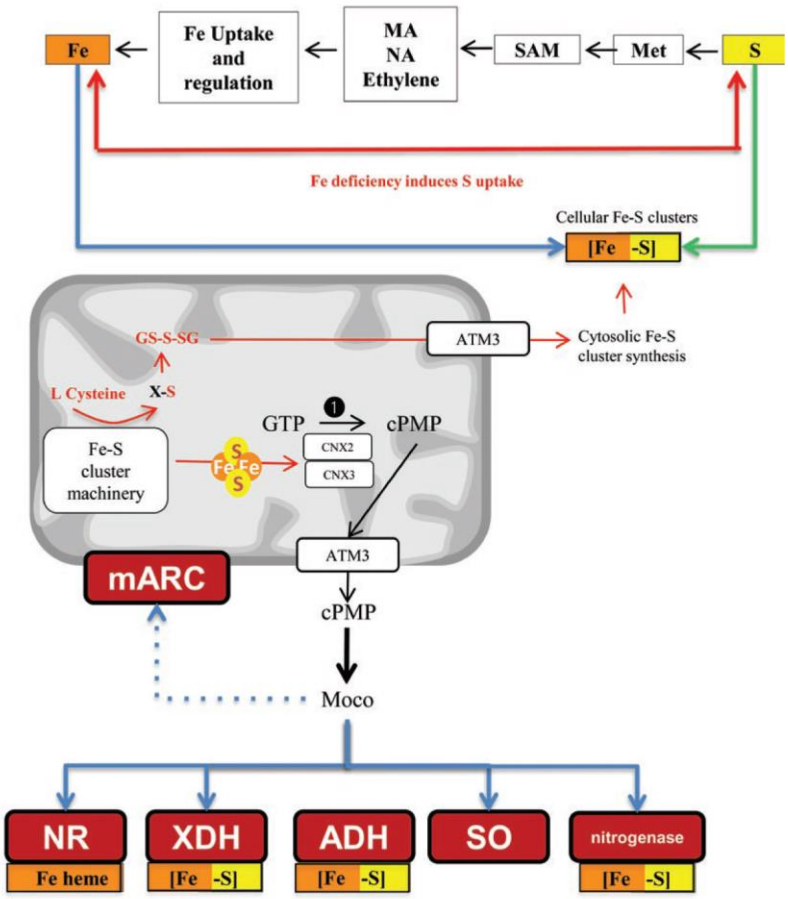


Crosstalk between S, Fe, Cu, Zn, and Mo during Mo co-factor (Moco) synthesis. Interactions of these nutrients are presented at the biochemical level (the steps in Moco synthesis and the catalytic proteins required) and at the level of gene-expression regulation (SULTR1.1, SULTR1.2, MOT1, CNX1). Under deficiencies of S, Fe, and Mo, the increase in Mo uptake seems to be an effect of the up-regulation of BnaSutr1.1 and BnaSutr1.2, which encode root sulfate transporters. In contrast, under Cu and Zn deficiencies, accumulation of Mo might be due to feedback signals from disturbances to Moco synthesis (due to low Cu and Zn contents), which could induce up-regulation of BnaMot1 (encoding the MOT1 transporter). The involvement of S, Fe, Cu, Zn, and Mo are presented sequentially in the four steps of the Moco biosynthesis pathway. (1) The proteins CNX2 and CNX3 catalyse the conversion of GTP to cPMP. cPMP is then exported from mitochondria by the mitochondrial ABC transporter ATM3. (2) In the cytosol, MPT synthase composed of CNX6 and CNX7 subunits transfers two atoms of S to cPMP to form MPT. MPT synthase is then sulfurated again by the MPT synthase sulfurase (CNX5), which contains one Zn atom per monomer. At the end of this step, an atom of Cu is bound to MPT to protect the reactive dithiolate before the insertion of Mo. (3) MPT is activated by adenylation to form MPT-AMP. This step is Mo- and Zn-dependent. (4) In the final step, MPT-AMP is transferred to the CNX1-E domain, which cleaves the adenylate from MPT and then catalyses the insertion of Mo in place of Cu to form Moco. ATM, ABC transporters of the mitochondria; cPMP, cyclic pyranopterin

monophosphate; [Fe-S], iron-sulfur cluster; MOT, molybdenum transporter; MPT, molybdopterin; MPT-AMP, adenylated molybdopterin; SULTR, sulfate transporter. Adapted from Billard et al. (2014) and Maillard et al. (2016a, 2016b).
Fig. 5.

S and Fe crosstalk

Several studies have demonstrated some close relationships between Fe and S nutrition, suggesting common regulatory mechanisms for the homeostasis of these two elements (Forieri et al., 2013). It has been shown that responses induced by Fe deficiency partly mimic the response to S deficiency, such as a strong increase in the expression of several sulfate transporter genes in durum wheat (Ciaffi et al., 2013), tomato (Paolacci et al., 2014; Zuchi et al., 2015), and in oilseed rape, along with an increased S uptake. On the other hand, Fe-use efficiency is usually increased under an adequate S supply in several cultivated species (Zuchi et al., 2009, Ciaffi et al., 2013). Such results might be due to S being required for the synthesis of SAM (Fig. 6), which is an intermediate molecule of the methionine cycle (Met), through which Met is supplied for ethylene production (Miyazaki and Yan, 1987). In addition, SAM is a precursor of important compounds for Fe homeostasis, such as phytosiderophores (mugineic acids, MA) and nicotianamine (NA) (Higuchi et al., 1999).
Fig. 6.



Integration of S and Fe interplay in Mo homeostasis in plants. Top: S is required for methionine (Met) and S-adenosyl-L-methionine (SAM) synthesis, and these act as precursors for the synthesis

of mugineic acids (MA), nicotianamine (NA), and ethylene. These compounds play a crucial role in Fe deficiency-induced responses in plants. In addition, Fe deficiency induces S uptake in several plants (see text). On the other hand, Fe and S join together to form Fe-S clusters in the cell. Bottom: Fe-S cluster assembly takes place in mitochondria, as does the synthesis of cyclic pyranopterin monophosphate (cPMP) (see Fig. 5), which is mediated by an Fe-S cluster-dependent protein (CNX2). The ATM3 mitochondrial transporter mediates the export from mitochondria to the cytosol of both cPMP and sulfur-containing metabolites (identified as GS-S-SG) that are required for the cytosolic assembly machinery. Biosynthesis of Mo co-factor (Moco) is finalised in the cytosol (see Fig. 5) and subsequently it is targeted to Mo-dependent enzymes: nitrate reductase (NR, which also requires Fe-heme); xanthine dehydrogenase (XDH, which also requires Fe-S clusters); aldehyde dehydrogenase (ADH, which also requires Fe-S clusters); sulfite oxidase (SO); nitrogenase (in rhizobia bacteria, and also requires Fe-S clusters); and mitochondrial amidoxime reducing component (mARC). The dotted line indicates that mARC localisation is currently not well characterised in plants.
Fig. 6.

Plants have evolved with two main Fe uptake strategies: (1) the Fe(III)-reduction-based mechanism, which is activated mainly by dicots and non-grass monocots (named strategy I plants), and (2) the Fe(III)-chelation-based mechanism, which is induced in grasses (named strategy II plants). In this context, the observed interplay in grasses between S and Fe might be due to a reduction in phytosiderophore synthesis and release under S limitation, while for strategy I plants, the interaction could be linked to impaired ethylene and NA production. In Arabidopsis, numerous connections have been observed between S and Fe metabolism at both transcriptomic and metabolomic levels that are specific for these nutrients (Fiorieri et al., 2017). Interestingly, Fe deficiency controls a distinct subset of genes involved in S homeostasis but these are not regulated by S deficiency, and this means that independent signal transduction cascades could also control the regulation of S–Fe interplay (Fiorieri et al., 2017). Such specific co-regulation of S and Fe homeostasis relies on the synthesis of Fe-S clusters (Fig. 6), which are essential for numerous catalytic proteins (Balk and Schaedler, 2014). Indeed, according to a recent classification of Fe-requiring enzymes (FeREs) in plants, Fe-S cluster-dependent enzymes belong predominantly to four of the six FeRE categories (Vigani and Murgia 2018).
Iron chemistry is basically related to its two oxidation states in aqueous solution, Fe(II) and Fe(III). Their interconversion facilitates many electron-transfer reactions that are needed in cell biology (Sánchez et al., 2017). The Fe(II/III) redox potential depends on the nature of the coordinated atoms and Fe can therefore be suitable to participate in various processes involving electron-transfer reactions. Fe(II) and Fe(III) are mainly found in 6-coordinate molecules with octahedral geometry. However, in most Fe/S co-factors, Fe is present as [2Fe-2S], cuboidal [3Fe-4S], and [4Fe-4S] in a distorted tetrahedral coordination environment (Pandelia et al., 2015). At least six types of Fe-S clusters have been described and are found in plastids, mitochondria, nuclei, and the cytosol, and have the ability to transfer electrons and participate through their association with different proteins in photosynthetic and respiratory electron transport in thylakoid membranes and in the inner mitochondrial membrane, respectively (Lu, 2018). The complex assembly of Fe-S clusters is tightly regulated due to the toxicity of free Fe and it has been shown as being influenced by Fe and S availability (Fiorieri et al., 2013).

Overall, the synthesis of Fe-S clusters involves the action of scaffold proteins interacting with Fe- and S-delivery proteins. While it is well known that S is derived from cysteine residues through the activity of cysteine desulfurases, Fe is delivered to Fe-S cluster assembly through the involvement of frataxin (Gomez-Casati et al., 2018, and references therein). Once formed, Fe-S clusters are then delivered to the recipient proteins in the appropriate sub-cellular compartment (no less than nine different carriers have been identified so far) (Lu, 2018). In plant cells, the Fe-S cluster assembly machinery is compartmentalised between three systems: the S mobilisation pathway (SUF), the Fe-S cluster (ISC) machinery, and the cytosolic Fe-S cluster assembly (CIA) machinery for plastidial, mitochondrial, and cytosolic/nuclear Fe-S proteins, respectively. In addition, the ISC machinery provides glutathione persulfide to the CIA machinery via an export system mediated by the ATM3 transporter (Schaedler et al., 2014). Such findings indicate that mitochondria play a more central role in the synthesis of cellular Fe-S clusters and thereby represent an important cellular compartment where S interacts with Fe (Fig. 6).

It has recently been observed that Fe or S deficiency, alone or combined, induce mitochondrial dysfunction in tomato roots (Vigani et al., 2018). In particular, Fe and S deficiency impair the respiratory chain in a similar way, while they differentially affect Krebs-cycle-related activities, with Fe deficiency being associated with a strong accumulation of citric acid relative to S deficiency. Based on the correlations that Vigani et al. (2018) found between citrate levels and some Fe and S deficiency-induced genes, they proposed that this organic acid may form a pivotal signal in Fe and S sensing and signalling. Such observations indicate that impairment of the respiratory chain might be the source of general nutrient-deficiency signals, whereas alterations to the Krebs cycle might be the source of specific nutrient-deficient signals. Thus, it has been hypothesised that mitochondrial dysfunctions occurring under Fe and S deficiency might be involved in the regulation of Fe and S deficiency-induced responses in plants (Fiorieri et al., 2013, 2017; Vigani and Briat, 2015; Vigani et al., 2018).

Mitochondria indeed represent an important cellular compartment where S interacts with other micronutrients. As already noted, cPMP (the Moco precursor) is synthesised in mitochondria by the activity of CXN2 proteins, which require Fe-S clusters (Fig. 6). Recently, a mutual interaction between Fe and Mo in mitochondria has been observed in plants (Vigani et al., 2017). Such crosstalk demonstrates that the accumulation of Mo in Fe-deficient mitochondrial might be linked to the increased synthesis of mARC, opening a question about the role of such Mo-dependent enzymes in Fe homeostasis.

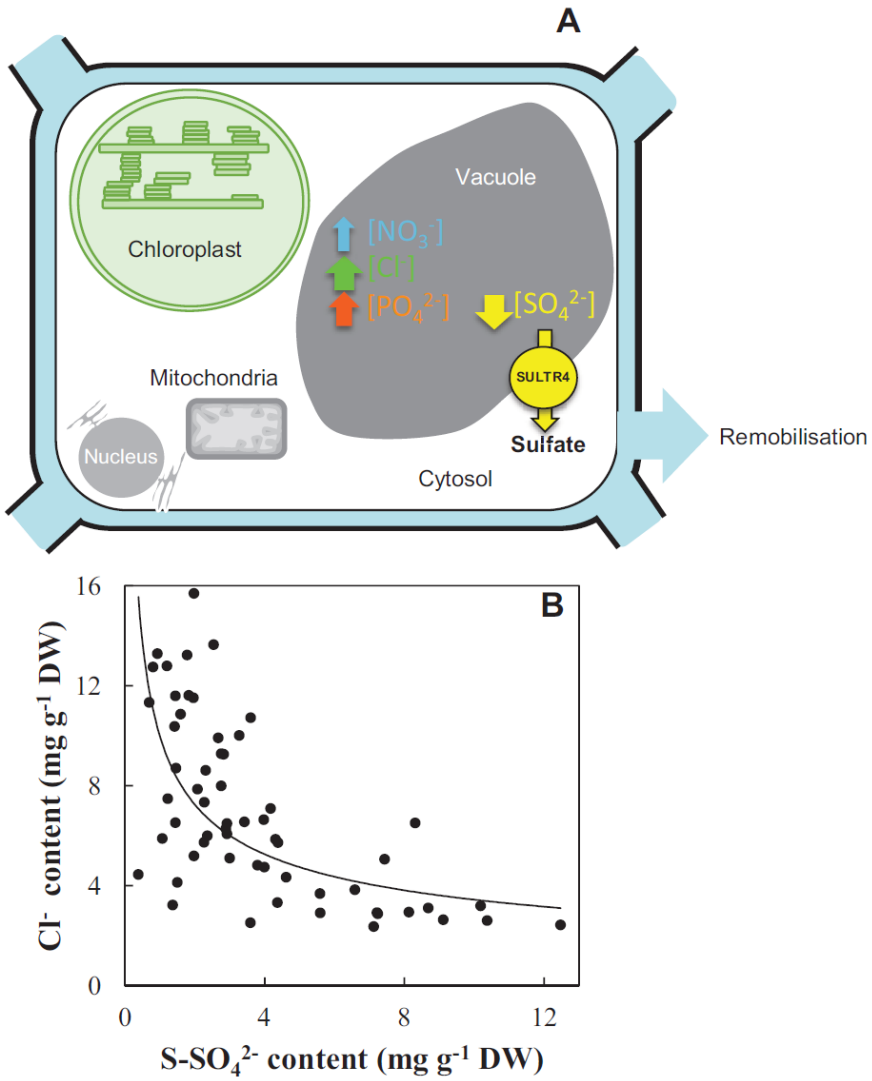
Mitochondria are organelles with a high micronutrient demand due to metallic co-factors being involved with the electron-transport chain and with other proteins essential for key metabolic activity. The most important metals present in plant mitochondria are Fe, Zn, Cu, Mn, Mo, and Co, which constitute the mitochondrial metallome (Tan et al., 2010; Nouet et al., 2011; Vigani and Hanikenne, 2018). Considering that S represents an essential macronutrient for mitochondrial function, that S interacts with Fe and Mo, and that Fe, Cu, Zn, and Mo strongly interact with each other, mitochondria might be considered as important players in nutrient interplay in plants.

The osmotic contribution of sulfate can be replaced by other anions such as chlorite and phosphate

When S availability decreases during plant growth, sulfate is usually remobilised from leaf vacuoles (Fig. 7A) as a result of Sultr4.1 up-regulation, and this sustains the S requirements of other growing tissues or seed filling (Abdallah et al., 2010; Shinmachi et al., 2010; Sorin et al., 2015). As an anion, sulfate makes a significant contribution as an osmoticum, for example accounting for around 10% of the leaf osmotic potential in leaves of B. napus (Sorin et al., 2015).

When a plant is fully deprived of sulfate supply, sulfate remobilisation is osmotically over-compensated by an accumulation of other anions (such as chlorine, phosphate, nitrate, and some amino acids; Fig. 7A) and the leaf osmotic potential can drop by 40%, which is certainly the case in plants grown in hydroponic conditions with no mineral limitation other than S. Under field conditions and using about 80 agricultural plots, Etienne et al. (2018) found strong linear correlations in B. napus between S and sulfate, P and phosphate, and Cl and chloride, but not between nitrate (usually found at low levels) and N. For the first three nutrients, their mineral form may account for up to 90% (as chloride), 70% (as sulfate), and 43% (as phosphate) of the total Cl, S, and P leaf contents, respectively. This suggests that sulfate, chloride, and phosphate may act as leaf osmotica under field conditions and that their accumulation is tightly linked. Nevertheless, only chloride and sulfate are negatively correlated under field conditions (Fig. 7B; Etienne et al., 2018), the accumulation of the former occurring mostly at low levels of sulfate, resulting from lower S fertilisation. A similar accumulation of chloride and of phosphate but to a lesser extent was also found in other cultivated species subjected to S deficiency, such as wheat, maize, and tomato (Etienne et al., 2018). Again, it has been proposed that the ratio of [S]/([Cl]+[P]) in leaves could be used as a proxy to evaluate S nutrition in cultivated plants, as these three elements can be easily quantified simultaneously using a portable X-ray fluorescence analyser. However, how the accumulations of chloride, phosphate, and sulfate are coordinated in the vacuole remains difficult to explain. For example, it has been reported that the expression patterns of genes encoding tonoplastic anionic transporters such as ClCa or ClCb, which are potentially involved in Cl– transport, are similar in S-deficient and control plants (Sorin et al., 2015).

Fig. 7.



(A) Vacuolar accumulation of Cl–, NO3–, and PO43– as a result of SO42– remobilisation from the vacuole during S deprivation. (B) Relationships between contents of Cl– and S-SO42– in leaves of Brassica napus. The data were obtained from plants grown in experimental field plots receiving different fertilization with N and S (0, 12, 36 kg-S ha–1). Redrawn from Etienne et al. (2018).
Fig. 7.

Modelling approaches for crop responses to S under other mineral constraints
The specificity of modelling crop S responses during interactions with other nutrients
Most crop models that are currently used were designed to consider single-nutritional limitations under climatic constraints such as temperature, radiation, or carbon dioxide, the variations of which are expected to increase in the coming decades. Historically, mostly N or P were targeted and little attention was paid to management of S fertilisation until the first signs of soil-S oligotrophy began to be observed following the implementation of environmental policies to reduce S-rich industrial emissions (protocols of Helsinki, 1985; Oslo, 1994; Kyoto, 1997). For high S-demanding crops of the Brassicaceae, modelling approaches have recently been proposed that

predict crop responses under S-limiting conditions that are combined with climatic variables, such as radiation and temperature (Brunel-Muguet et al., 2015; Poisson et al., 2018a;, 2018b).
Most models predict crop responses to mineral limitations based on their vital requirement for producing dry matter. Critical dilution curves are thus the central equations that drive downstream processes, such as remobilisation towards growing sinks. One characteristic of S nutrition is its excessive accumulation in vacuoles, mainly as sulfate (Blake-Kalff et al., 1998) without straightforward assimilation into organic forms. Consequently, critical S-dilution curves require consideration of the concentration of assimilated S, which is the S concentration that is not in mineral form, and this contrasts with critical N-dilution curves calibrated for C3 and C4 crops (Greenwood et al., 1990; Juste et al., 1994; Lemaire and Gastal, 1997; Colnenne et al., 1998; Debaeke et al., 2012). Although similar allometric power equations are used widely for N, critical S-dilution curves cannot be obtained using total S concentration but can be generated by deducing the concentration of S from sulfate (S-SO42–), as performed by Brunel-Muguet et al. (2015).
In the light of strong evidence for the tight interactions between S and major minerals (such as N, P, K), predictive models that couple several mineral limitations need to be developed in order to better monitor global fertilisation strategies. However, such modelling perspectives are still hampered by conventional modelling approaches. Indeed, prediction of plant growth is still generally based on Liebig's law of the minimum, which states that growth is driven by the most limiting factor (see Salisbury, 1992), and this is based on the conventional hypothesis that plant performance is limited by a single nutrient at a time. Thus, co-limitation of minerals cannot be applied in such models, even though several lines of evidence have indicated non-additional effects of various limiting elements in a wide range of ecosystems (Elser et al., 2007; Harpole et al., 2011). Emerging approaches in crop and livestock models have attempted to predict growth responses to combined stresses in a co-limiting scheme (Sperfeld et al., 2012; Agren et al., 2012). As already detailed, S limitation affects the metabolism of a myriad of other elements, ranging from uptake to transport, and from assimilation to homeostasis. Co-limitation has been classified into three categories as defined by Saito et al. (2008) and extended by Agren et al. (2012), namely: homeostasis co-limitation where minerals can replace each other (e.g. sulfate versus chloride); biochemically dependent co-limitation where the uptake of one mineral is determined by the availability of others; and 'serially linked nutrients' (Agren et al., 2012), which allows control of the rate of growth by one mineral to be determined by the control of the rate of another process by another mineral. The underlying approach to modelling co-limitation has been defined as the 'multiple limitation hypothesis' (Bloom et al., 1985; Gleeson and Tilman, 1992), which basically defines smooth switches from one mineral limitation to another based on the dynamic strength of each mineral limitation as defined as the supply:demand ratio for each nutrient (Sperfeld et al., 2012). Refining conventional modelling concepts should therefore be targeted towards consideration of S interactions in co-limiting conditions, which are actually the more usual conditions expected in agriculture.
Modelling perspectives for interactions between S and other minerals
Another approach to integrating interactions with other nutrients is the implementation of existing process-based models where equations underlie specific processes (e.g. uptake, assimilation, and remobilisation). In the process-based SuMoToRI model (Brunel-Muguet et al., 2015), equations are defined to simulate the dynamics of an S-mobile pool used for remobilisation towards growing sinks in winter oilseed rape. This model predicts the daily increase in leaf area, dry matter, and mobile-S:structural-S ratio in the leaves. It can be assumed that S-responses to different processes are modulated by supplies of other nutrients, and therefore scaling S-related

equations to another mineral constraint such as N can be incorporated by introducing a coefficient to modify the parameter values relative to N availability. Preliminary modelling studies in oilseed rape have been undertaken to illustrate the need to integrate N-associated processes (mainly uptake, assimilation, and remobilisation) in this modelling framework. In this work (E. Poisson, Normandie Université, unpublished results), simulations with the SuMoToRI model were performed under several combinations of S and N supplies and compared to observations from greenhouse experiments. Under non-limiting N supply, regardless of the levels of S supply (corresponding to 30–100% of the usual recommendation applied at bolting) the S contents in the leaves were correctly predicted, whereas under limiting N supplies they were under-estimated when combined with non-limiting S supply and over-estimated when combined with limiting S supply. These results not only illustrate the impact of N supply on S-related processes but also the importance of balancing the mineral S:N ratio, as previously highlighted in soybean (Divito et al., 2015, 2016), oilseed rape (Blake-Kalff et al., 2000), and wheat (Blake-Kalff et al., 2002; Reussi Calvo et al., 2008). In the light of these results and our broad knowledge of S interactions with other minerals, research should be directed towards modelling more integrative S responses by incorporating the main physiological effects of S-driven growth processes. Constructing a modelling framework where the starting equations are based on S-driven growth processes could be proposed. The influence of other minerals on these processes, i.e. S uptake, transportation, and storage/sequestration, should then be described quantitatively to further consider the one-way interaction (i.e. effects of minerals on S responses). In a second step, the effects of S deficiency on related processes with other minerals should be targeted to extend the S fertilisation conditions, and consequently enable the crop model to be used as a predictive management tool under low S-inputs. Interactions between S and Mo, Se, and Fe should be prioritised because of their consequences for key mechanisms driven by S compounds. Thus, there are new avenues of modelling that could be developed alongside more detailed characterisation of these numerous interactions.

Conclusions

In this review we have highlighted the complexity of interactions occurring between S and other nutrients. In particular, S displays a strong link with transition metals such as Fe and Mo. Therefore, a complete understanding of ionome homeostasis requires a thorough investigation of the dynamics of the nutrient networks in plants. Such an approach will provide information on new factors that play a role in nutrient homeostasis and new information that will be useful for defining models of nutrient interactions. However, as we have discussed in this review, studies on the interplay between S and other nutrients should be addressed at the level of the whole plant, the individual tissues, and the cellular compartments. To properly decipher nutrient networking, we recommend consideration of the fact that nutrient interactions are a dynamic process and the severity of the deficiency of a given nutrient might differentially impact the homeostasis of other nutrients, and that nutrient interactions might change in different plant tissues or within different cellular compartments. Furthermore, investigating interactions amongst nutrients is also crucial for understanding microbe interactions with plants, with nutrient dynamics at the plant/soil interface representing an important focal point for identifying new mechanisms that regulate plant–microbe associations.

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