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Autophagy as a possible mechanism for micronutrient remobilization from leaves to seeds

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Seed formation is an important step of plant development which depends on nutrient allocation. Uptake from soil is an obvious source of nutrients which mainly occurs during vegetative stage. Because seed filling and leaf senescence are synchronized, subsequent mobilization of nutrients from vegetative organs also play an essential role in nutrient use efficiency, providing source-sink relationships. However, nutrient accumulation during the formation of seeds may be limited by their availability in source tissues. While several mechanisms contributing to make leaf macronutrients available were already described, little is known regarding micronutrients such as metals. Autophagy, which is involved in nutrient recycling, was already shown to play a critical role in nitrogen remobilization to seeds during leaf senescence. Because it is a non-specific mechanism, it could also control remobilization of metals. This article reviews actors and processes involved in metal remobilization with emphasis on autophagy and methodology to study metal fluxes inside the plant. A better understanding of metal remobilization is needed to improve metal use efficiency in the context of biofortification.

Keywords: transition metal, isotopic labeling, nutrient use efficiency, leaf senescence, nutrient fluxes, *atg*, Fe, Zn

INTRODUCTION

Micronutrients, such as metals, are essentials for cell functions. Zinc (Zn), which exists only as divalent cation, plays an important role in protein structure and function thank to its Lewis acids properties. Transition metals such as iron (Fe), copper (Cu), or manganese (Mn), which have unpaired electrons that promote their involvement in oxido-reduction reactions, are used in a wealth of biological processes (Pierre and Fontecave, 1999). A third of the proteins characterized at the structural level are metalloproteins, highlighting the need of metals for cell functions (Finney and O'Halloran, 2003).

In plants, transition metal functions are mainly associated to energy production mechanisms, thereby about 80% of Fe in mesophyll cell is localized in chloroplasts (Nouet et al., 2011). Fe is essential for chlorophyll synthesis, nitrogen fixation, DNA replication, reactive oxygen species (ROS) detoxification, and electron transport chain in both mitochondria and chloroplasts (Nouet et al., 2011; Yruela, 2013). Mn plays a central role in the photosystem II (PS II) where it catalyzes water oxidation (Tommos et al., 1998). This element is also involved in sugar metabolism, Mn-superoxide dismutase (SOD), and chloroplastic enzymes such as decarboxylases and dehydrogenases (Luk and Culotta, 2001; Horsburgh et al., 2002; Aggarwal et al., 2012). Cu is integrated into plastocyanines involved in electron transfer of chloroplasts (Yruela, 2013). It plays also an essential role in the cytochrome oxidase of mitochondria (Bleackley and Macgillivray, 2011). Zn is required for carbon fixation through the carbonic anhydrase (Badger and Price, 1994). It is also needed for the Cu/Zn-SOD, transcriptional regulation by zinc-finger DNA binding proteins and for the turnover of PSII in chloroplasts (Kurepa et al., 1997; Bleackley and Macgillivray, 2011; Lu et al., 2011). Therefore, plants need metals to achieve vital functions in all their organs.

Among all plant organs, seed is a special one because it has to store metals required for germination and during the first days of seedling development. Hence in annual plants, seed formation is a crucial step in which plant sacrifices itself to store nutrients for its offspring. Seed filling depends on nutrient originating from *de novo* uptake by roots or remobilization from senescent organs.

Here, we review genes and processes involved in metal remobilization during seed filling. We will discuss methodologies that can be used to study metal fluxes in plants and thereby determine the relative contribution of uptake and remobilization pathways. Autophagy is a ubiquitous process involved in cellular nutrient recycling. Because it was recently shown to play a critical role in nitrogen remobilization (Htwe et al., 2011; Guiboileau et al., 2012), this review focuses on autophagy as a potential mechanism to make metal available for subsequent remobilization during senescence.

ORIGIN OF SEED METALS: UPTAKE FROM SOIL VS REMOBILIZATION FROM SENESCENT TISSUES

CIRCULATION OF METALS INTO THE PLANT AND MICRONUTRIENT USE EFFICIENCY

Understanding metal seed filling requires knowledge on the general micronutrient pathways which was already summarized in several recent reviews (Pittman, 2005; Palmgren et al., 2008; Morrissey and Guerinot, 2009; Puig and Peñarrubia, 2009; Yruela,

2009; Pilon, 2011; Waters and Sankaran, 2011; Thomine and Vert, 2013).

On the whole, both uptake from soil and remobilization from senescent organs may participate in metal loading in seeds (**Figure 1**). To date, little is known about the contribution of metal remobilization from senescent organs to seed filling. In contrast, this topic is well documented regarding nitrogen. It was shown that uptake and fixation of nitrogen dramatically decrease at the onset of reproductive stage in cereals, oilseed rape and legumes (Salon et al., 2011). Accordingly, 50 to 90% of nitrogen grain of rice, wheat, or maize originate from leaf remobilization (Masclaux et al., 2001). This highlights that the importance of nitrogen remobilization for seed filling is conserved in most plants. However, some species, such as oilseed rape, have a low nitrogen remobilization capacity resulting in low nitrogen use efficiency (Schjoerring et al., 1995; Etienne et al., 2007).

As for nitrogen, it is necessary to better understand metal remobilization from senescent organs during seed filling with the aim to increase micronutrient use efficiency in the context of intensive agriculture, fertilization limitations, and biofortification. This is especially important as metal availability may become limiting under certain environmental conditions (drought, low temperature) and soil characteristics (low metal content, high salt content, ionic unbalance, low pH, high bicarbonate concentration; Chen and Barak, 1982; Karamanos et al., 1986; Graham, 1988; Alloway, 2009).

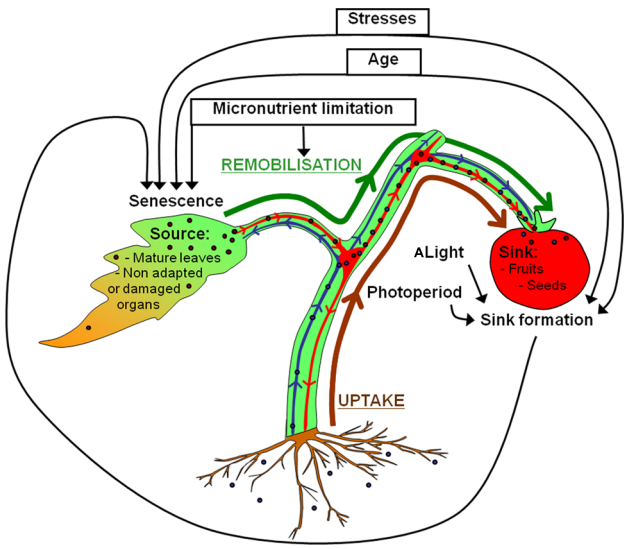

FIGURE 1 | Uptake and remobilization pathways involved in seed filling with emphasis on source-sink relationships. Micronutrients from the rhizosphere (brown arrow) are taken up into roots and transported to the xylem vessels (shown in blue). After xylem loading, micronutrients are translocated into shoots for subsequent unloading. Micronutrients located in the xylem can also be unloaded into the xylem parenchyma of nodes to be transferred to phloem vessels (shown in red) by specific transporters (Sondergaard et al., 2004; Tanaka et al., 2008; Yamaji and Ma, 2009). This is essential for seed filling which is only achieved by the phloem sap (Patrick and Offler, 2001). Phloem micronutrients are unloaded to fill seeds. Because seed filling is also achieved by nutrient remobilized from senescent tissues (green arrow), seed formation requires close synchronization between sink formation and source organ senescence. Age, biotic and abiotic stresses contribute to orchestrate nutrient mobilization during leaf senescence with the formation of reproductive organs and seed filling (black arrows). Light and photoperiod act indirectly on leaf senescence by stimulating the development of the reproductive organs.

METHODOLOGIES TO DETERMINE NUTRIENT FLUX

The most common way to study nutrient fluxes within the plant is to determine the "apparent remobilization" which consists in the measurement of the total amount of element of interest present in different plant organs at different times (Masclaux-Daubresse et al., 2010). However, this approach does not provide sufficient resolution and does not allow distinguishing nutrients coming from different pathways, such as nutrient uptake from soil and nutrient remobilization from senescent leaves.

The most appropriate approach to study short-term accumulation, uptake from soil and fluxes between tissues is the use of isotopes as tracers. Isotopic labeling can be implemented with different protocols (Grusak, 1994; Wu et al., 2010; Erenoglu et al., 2011; Hegelund et al., 2012).

Metal fluxes may be monitored by pulse-chase labeling using radioactive or stable isotopes. The ^{59}Fe, ^{65}Zn, and ^{68}Zn radioisotopes have been used for pulse labeling on specific organs followed by a chase period to facilitate the identification of source organs contributing to seed filling in peas, wheat and rice (Grusak, 1994; Wu et al., 2010; Erenoglu et al., 2011; Zheng et al., 2012). Following this approach, it was demonstrated that nutrient supply can affect Zn remobilization in wheat (Erenoglu et al., 2011). In rice, differences in Zn remobilization efficiency between genotypes were observed using isotopic pulse-chase on specific organs (Wu et al., 2010).

Recently, pulse labeling using very short life ß$^+$ radioisotope like ^{52}Fe, ^{52}Mn, and ^{62}Zn has been used to image metal fluxes within a plant *via* a real-time and non-destructive technique called Positron-Emitting Tracer Imaging System (Kume et al., 1997; Tsukamoto et al., 2006; Tsukamoto et al., 2009).

Non-radioactive isotope is also used for pulse labeling on specific organs. Application of ^{65}Cu to one individual leaf of rice allowed to study Cu redistribution between the different leaves during vegetative stage (Zheng et al., 2012). Non-radioactive isotopes can be also added in the nutrient solution for labeling plants early during development in order to monitor nutrient movement during vegetative stages or later at reproductive stage to study remobilization and seed filling. Using Zn isotopes, this pulse-chase approach has been used to quantify the effect of nutrient limitation on Zn fluxes between organs in rice and wheat (Wu et al., 2010; Erenoglu et al., 2011). Moreover, ^{70}Zn pulse-chase labeling combined with laser ablation-inductively coupled plasma-mass spectrometry has provided a spatial distribution of Zn within wheat seeds revealing zinc transport barriers during grain filling in wheat (Wang et al., 2010).

Long term labeling in nutrient solution may be performed to address the contribution of uptake from soil to organs during a specific developmental stage, with respect to the contribution of endogenous remobilization. Continuous application of ^{68}Zn provided evidence that Zn uptake before anthesis contributes to

more than 50% to the total Zn grain content in rice (Wu et al., 2010). Shorter continuous labeling can also be used to determine the uptake capacity by measuring isotope accumulation in roots (Hegelund et al., 2012) or isotope depletion in the nutritive solution (Erenoglu et al., 2011).

Isotopic labeling is an essential tool to study metal fluxes within the plant but require the availability of enriched isotopes and adequate analytical tools. Initially, isotopic labeling was mainly performed using radioactive isotope despite the risk for humans. Nowadays, enriched stable isotopes are more and more accessible at least for Fe, Ni, Cu, Zn, and Mo. They represent a healthier and less restrictive alternative but their analysis requires the use of mass spectrometry, such as inductively coupled plasma-mass spectrometry.

THE COUPLING BETWEEN SENESCENCE AND MICRONUTRIENT REMOBILIZATION

CONTROL OF SENESCENCE AND REMOBILIZATION AT THE WHOLE PLANT LEVEL

Senescence is an active process controlled by age whereby sink tissues performing photosynthesis and anabolism become source tissues undergoing catabolism (**Figure 2**). Senescence makes nutrients available for further plant organs (Hörtensteiner and Feller, 2002), contributing to nutrient use efficiency. Optimal remobilization requires close synchronization between sink formation and source organ senescence (**Figure 1**). It was observed that the removal of sink tissues delays senescence in oilseed rape, soybean and wheat and decrease nitrogen remobilization in oilseed rape and soybean (Patterson and Brun, 1980; Crafts-Brandner and Egli, 1987; Noquet et al., 2004; Htwe et al., 2011). However, senescence and remobilization are also controlled by other parameters such as nutrient availability (**Figure 1**). In *Arabidopsis*, nitrogen limitation triggers leaf senescence (Lemaître et al., 2008). In wheat, remobilization of Fe and Zn from flag leaves to seeds is increased under nutrient-limiting conditions (Waters et al., 2009; Wu et al., 2010; Sperotto et al., 2012b). Conversely continuous nutrient uptake during seed formation may account for low nutrient remobilization in some species (Masclaux-Daubresse and Chardon, 2011; Waters and Sankaran, 2011). However, an opposite behavior was observed in barley plants for which remobilization increased upon high Zn supply. This illustrates the diversity of Zn management at the whole plant level (Hegelund et al., 2012). Moreover, other abiotic and biotic stresses such as pathogen attack, high salinity, drought, low temperature, modifications of light intensity, and quality can also cause premature senescence and remobilization (Nooden et al., 1996; Buchanan-Wollaston, 1997; Gan and Amasino, 1997). Because they are sessile, plants developed high plasticity to respond to environment conditions, triggering cell death and remobilization in order to save nutrients and produce more adapted organs and tissues.

CONTROL OF SENESCENCE AND REMOBILIZATION AT THE MOLECULAR LEVEL

Transcript analysis, comparing green and senescing leaves, led to the identification of senescence-associated genes (SAG) in different species (Hensel et al., 1993; Buchanan-Wollaston, 1994; Smart et al., 1995; Guo et al., 2004; Buchanan-Wollaston et al., 2005; van der Graaff et al., 2006; Breeze et al., 2011). Irrevocably, the expression of genes encoding cysteine proteases is strongly induced in senescent leaves (Hensel et al., 1993; Smart et al., 1995; Bhalerao et al., 2003; Andersson et al., 2004; Guo

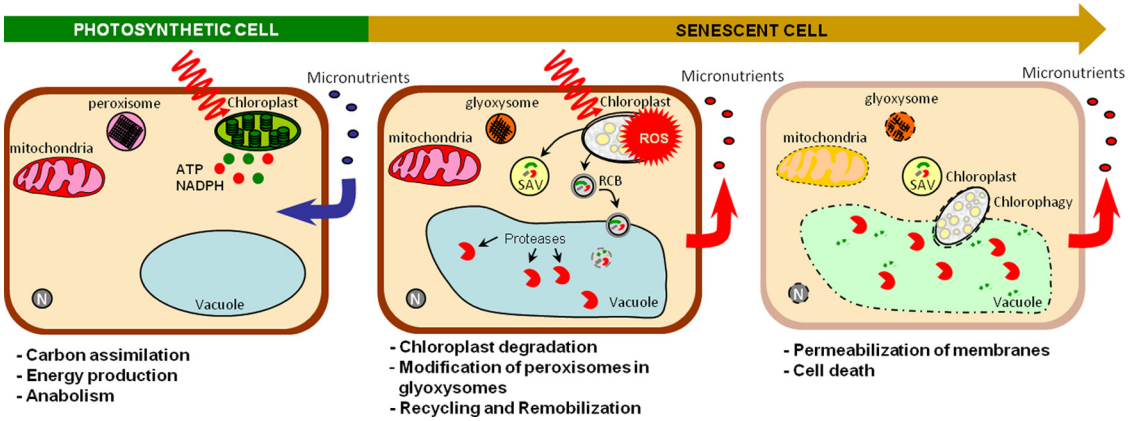

FIGURE 2 | Sink/source transition at the cellular level. Active photosynthetic cells perform carbon fixation, energy production and anabolism and require micronutrients for these functions. Senescence modifies these sink cells into a source cells undergoing catabolism. Intense catabolism activities and nutrient recycling occurs in chloroplasts, cytosol, and vacuole allowing nutrient remobilization. Chloroplasts, which concentrate a large part of metals, are first affected (Zavaleta-Mancera et al., 1999). Pigment degradation directly takes place in chloroplasts (Hörtensteiner et al., 1995; Park et al., 2007). However, stromal proteins are degradated into the central vacuole through rubisco containing body (RCB: autophagosome) or into senescence associated vacuoles (SAV) through an ATG-independent route which is not well understand yet (Hörtensteiner and Feller, 2002; Ishida et al., 2008; Ishida et al., 2013). These dismantling mechanisms decrease chloroplast seize enabling whole chloroplast degradation via chlorophagy (Ishida et al., 2013). Peroxisomes are modified to glyoxysomes, which produce energy and soluble sugars from lipid catabolism (Buchanan-Wollaston, 1997; del Rio et al., 1998). Mitochondria that remain intact until late after senescence onset, are in turn degraded when the energy demand decreases (Yoshida, 2003). Finally, membrane permeabilization causes loss of cytoplasm that finally leads to death. ROS, reactive oxygen species; SAV, senescence-associated vacuoles; RCB, rubisco containing body; N, nucleus.

et al., 2004; Breeze et al., 2011). As expected, these analyses confirmed induction of genes involved in hormonal pathways (Andersson et al., 2004; van der Graaff et al., 2006; Breeze et al., 2011). Indeed, senescence is regulated by the balance between senescence promoting hormones, namely jasmonic acid, abscisic acid, salicylic acid, and ethylene, and senescence repressing hormones such as cytokinins, auxins, and gibberellins (van der Graaff et al., 2006). As hormones, sugars are known to act as signaling molecules and several lines of evidence indicate that they also contribute to senescence regulation. Sugar concentrations rise in senescent leaves. Moreover, overexpression of hexokinase, a sugar sensor, accelerates senescence whereas antisense expression delays senescence in *Arabidopsis* (Nooden et al., 1997; Masclaux et al., 2000; Xiao et al., 2000; Watanabe et al., 2013).

Genes coding metal ion binding proteins such as metallothioneins, ferritins, zinc-finger proteins, metalloproteases (Ftsh) and metal transporters were also frequently found to be upregulated in senescent leaves (Buchanan-Wollaston, 1994; Bhalerao et al., 2003; Andersson et al., 2004; Guo et al., 2004; Zelisko et al., 2005). This may illustrate the involvement of metals in degradation mechanisms and/or the importance of their remobilization (Breeze et al., 2011). Furthermore, these transcriptomic analyses highlighted the significant induction of autophagy related genes (*ATG* genes) and genes encoding NAC and WRKY transcription factors (Andersson et al., 2004; Guo et al., 2004; van der Graaff et al., 2006; Breeze et al., 2011). Whereas NAC have already been demonstrated to be involved in micronutrient remobilization during senescence (Olmos et al., 2003; Guo and Gan, 2006; Uauy et al., 2006; Sperotto et al., 2009, 2010; Waters et al., 2009), nothing is known about the implication of *ATG* genes in this process.

ROLE OF AUTOPHAGY IN NUTRIENT RECYCLING AND REMOBILIZATION

INVOLVEMENT OF AUTOPHAGY IN NUTRIENT RECYCLING

Autophagy catabolizes cytoplasmic components that are no longer useful. It eliminates aberrant proteins and damaged organelles for the maintenance of essential cellular function by vacuole internalization mediated by double membrane vesicles called autophagosomes (Yoshimoto, 2012). Genes involved in autophagy (*ATG*) were first defined by a genetic screen in yeast (Matsuura et al., 1997), thereby molecular mechanisms have been well described on this organism (for reviews see Thompson and Vierstra, 2005; Bassham, 2007; Li and Vierstra, 2012; Yoshimoto, 2012). Most of these genes turned out to have conserved functions in all eukaryotic cells. They encode proteins involved in the induction of autophagy, membrane delivery for autophagosome formation, nucleation, expansion, and enclosure of autophagosomes (Thompson and Vierstra, 2005).

Autophagy can be triggered upon nutrient starvation and stress leading to intracellular remodeling, which allows plants to respond to environmental constraints (Yoshimoto, 2012). Accordingly, mutants impaired in *ATG* genes exhibit decreased growth associated with premature senescence when they develop under carbon or nitrogen starvation (Doelling et al., 2002; Hanaoka et al., 2002; Yoshimoto et al., 2004; Phillips et al., 2008; Chung et al., 2010; Suttangkakul et al., 2011). Plants defective in autophagy are thus unable to cope with nutrient starvation suggesting that autophagy is an important mechanism for nutrient use efficiency and cellular homeostasis.

AUTOPHAGY CONTROLS NUTRIENT REMOBILIZATION DURING SENESCENCE

During senescence, cytoplasmic components such as organelles are gradually dismantled and degraded. Autophagy is an essential degradation process for nutrient recycling and remobilization. Accordingly, up-regulation of *ATG* genes is observed during leaf senescence in *Arabidopsis* (Doelling et al., 2002; van der Graaff et al., 2006; Chung et al., 2010; Breeze et al., 2011) and the decrease of chloroplast number and chloroplast size during senescence is affected in *Arabidopsis atg4a4b-1* mutant (Wada et al., 2009).

Because of its key role in the degradation of cellular components during nutrient recycling and its up-regulation and involvement during senescence, it was hypothesized that autophagy could play a role in nutrient remobilization. During senescence, autophagy was shown to be involved in the degradation of chloroplasts and specifically of RuBisCO which is the most abundant leaf protein containing about 80% of the cellular nitrogen (**Figure 2**; Chiba et al., 2003; Ishida et al., 2008; Wada et al., 2009; Guiboileau et al., 2012; Ishida et al., 2013). In addition, pulse-chase experiments in which ^{15}N labeling was applied in nutrient solution during vegetative stage revealed a significant decrease of nitrogen remobilization from vegetative tissues to seeds in *atg* mutants. These results demonstrated that autophagy is required for nitrogen remobilization and seed filling (Guiboileau et al., 2012).

Chloroplast is the organelle where metals are most intensively used. Thereby about 80% of the cellular Fe is localized in chloroplasts (Nouet et al., 2011). Because autophagy is involved in the degradation of organelles, including chloroplasts, the role of autophagy in metal recycling in source tissues for remobilization to the seeds has to be considered. In plants, autophagy leads to the degradation of autophagosome cargo within the vacuole. Hence, tonoplastic metal efflux transporters are needed to retrieve metals from the vacuole. Interestingly, transcriptomic analyses that highlight autophagy induction during senescence in *Arabidopsis* leaf also show specific up-regulation of *NRAMP3*, a gene encoding a transporter involved in metal mobilization from vacuoles (Thomine et al., 2003; Lanquar et al., 2005, 2010; Breeze et al., 2011). Availability of metals in source tissues may therefore also be dependent on autophagy and subsequent mobilization from vacuole during senescence.

REMOBILIZATION AND AUTOPHAGY IN THE CONTEXT OF BIOFORTIFICATION

BIOFORTIFICATION TO IMPROVE HUMAN DIET

Key micronutrients are often not sufficiently available in human diet (Kennedy et al., 2003). Over 60% of the world population are Fe deficient and over 30% are Zn deficient (White and Broadley, 2009). Staple food crops such as cereal grains are poor sources of some mineral nutrients, including Fe and Zn. Thus, the importance of cereals in human diet accounts

in large part for micronutrients deficiencies (Gomez-Galera et al., 2010).

Biofortification aims at increasing the availability of key micronutrients such as Fe and Zn in crops (White and Broadley, 2009). For this purpose, conventional breeding and genetic engineering are performed in rice, which is the major staple crop in most countries affected by Fe-deficiency (Juliano, 1993; WHO, 2002; Sperotto et al., 2012a). Single or multiple metal homeostasis genes were already introduced in rice through genetic engineering to improve grain Fe content (Sperotto et al., 2012a). By pyramiding transgenes conferring strong sink strength in seeds, high metal translocation and enhancing phloem unloading during seed maturation, it was possible to increase Fe concentration by 4.4 in rice seeds (Masuda et al., 2012).

ENGINEERING AUTOPHAGY AS A NEW WAY FOR BIOFORTIFICATION

Another option to increase seed micronutrient content could be to improve their availability in source tissues for remobilization during seed formation. Himelblau and Amasino (2001) showed that senescence of *Arabidopsis* leaves only leads to a decrease by 40% of leaf concentrations of metals such as Mo, Fe, Cu, and Zn. Thus, about 60% of these micronutrients are not remobilized and can therefore not participate to seed filling. Up-regulating autophagy in source tissues specifically during seed formation could improve intracellular nutrient recycling and thereby increase the nutrient pool available for reallocation. However, because autophagy is not specific, this approach may increase seed yield without increasing Zn or Fe concentrations. To improve seed quality, up-regulation of autophagy should be combined with a strategy that specifically targets a metal, such as the expression of ferritin under the control of a seed endosperm promoter in the case of Fe (Sperotto et al., 2012a).

More than thirty genes are involved in autophagy (Yoshimoto, 2012). It might therefore not be straightforward to increase autophagy by overexpressing autophagy related genes during seed formation. However, autophagy is regulated at the post-transcriptional level by the target of rapamycin (TOR) kinase complex (Noda and Ohsumi, 1998; Kamada et al., 2000). Because TOR is a negative regulator of autophagy, its specific inhibition in vegetative tissues during seed formation may be the best approach to stimulate autophagy and nutrient recycling. On the other hand, TOR kinase complex is not a specific regulator of autophagy. It controls many others aspect of metabolism (Diaz-Troya et al., 2008). Besides, autophagy itself is not only involved in nutrient recycling. It also controls the hypersensitive response (Yoshimoto et al., 2009). Therefore, further investigations are necessary to determine if TOR inactivation during senescence is efficient for biofortification and to identify more specific regulators.

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