Molecular Regulation of Arbuscular Mycorrhizal Symbiosis

The cooperative and mutualistic interaction between plant roots and arbuscular mycorrhizal (AM) fungi from the phylum Glomeromycota is tightly regulated by both partners at the cellular, molecular and genetic levels, and it is highly dependent on environmental and biological variables.

1. Nutritional Regulation

The main sense and the success of the arbuscular mycorrhizal (AM) symbiosis basically resides in the mutual nutritional benefits obtained by both interacting partners, the plant and the AM fungus. Plants provide carbon (C) to AM fungi in form of carbohydrates and fatty acids, while AM fungi provide minerals, mainly inorganic phosphate (Pi) and nitrogen to the plants. It is logical to assume that the availability of the different nutrients is a key factor determining the establishment and development of the interaction.

Among the different exchanged nutrients, phosphate is the one that is thought to be the most important in the regulation of the AM symbiosis. Actually, high phosphate supply causes inhibition of root colonization from a very early stage, including hyphopodia formation [1][2], and high Pi negatively affects presymbiotic signalling [3]. Although less studied, nitrogen is also a nutritional determinant of the interaction. Nouri, et al.[4] have shown that N starvation reduces the negative effect of high Pi on the AM symbiosis, and premature arbuscule degeneration observed in plants mutated for genes encoding specific mycorrhizal Pi transporters is prevented at low N conditions in the media. Although researchers cannot discard a regulatory role of other mineral nutrients, they may have a minor importance in comparison to Pi and N. For example, in petunia plants inoculated with *Rhizophagus irregularis*, no AM development-sensitivity was detected for any of the alternative tested nutrients, including sulfate, calcium, magnesium, and iron [4].

Carbon availability (in form of sugars and lipids) from the plant to the AM fungus is also a factor determining AM development. In soybean plants, it has been shown that inoculation with AM fungus species exhibiting higher colonization rates, compared to those ones with lower AM colonization, is accompanied with an increased plant growth and with higher sugar contents, as well as a higher induction of genes related to sugar metabolism and transport [5]. Recent research has also revealed a regulatory role of lipids in the AM symbiosis. The reduced lipid transfer from hosts to AM fungi inhibits arbuscule formation [6].

2. Arbuscular Mycorrhizal Regulation by Hormones and Other Signalling Molecules

Clear evidence shows that AM symbiosis alters plant hormonal homeostasis and almost all phytohormones have a key regulatory role in the establishment and functionality of the AM symbiosis, as shown by many studies based on the application of hormone treatments or on the analysis of plants with alterations in hormone biosynthesis or signalling. Plant hormones have been reported to act from early stages in the presymbiotic signalling, to later stages (revised by [Pozo, et al. [7], Bedini, et al. [8], Liao, et al. [9]).

Before the physical contact between the AM fungus and the plant root, it is required a molecular communication between both symbionts. The key elements for this communication are strigolactones (SLs) from the plant side. Once these compounds are secreted from the root to the rhizosphere in response to Pi deficiency conditions [10][11], they serve as signals indicating the presence of a host receptive to be colonized by AM fungi. In this sense, many reports show that mycorrhizal colonization is significantly reduced in plant mutants defective for the biosynthesis and export of strigolactones [10][12][13][14]. Abscisic acid (ABA) is another apocarotenoid hormone with a regulatory role in mycorrhizal

root colonization. The ABA *sitiens* tomato mutants with reduced ABA concentrations showed a reduced AM colonization and a lower percentage of well-developed arbuscules [15][16], while mycorrhizal colonization and arbuscule intensity were promoted in ABA pre-treated potato plants [17]. Charpentier, et al.[18] showed a dual role of ABA on AM symbiosis in *Medicago*. Several reports suggest that the giberellin-DELLA complex also plays an essential role in the control of the symbiosis. Mycorrhizal development is ligated to the increased levels of GAs, and an increased expression of genes associated to their biosynthesis [19][20][21]. Experiments with pea mutants deficient in gibberelins, as well as exogenous GA treatment applied to rice and tomato plants support a negative regulatory role of GAs on mycorrhizal colonization [20][22][23]. Brassinosteroids are also thought to have a signalling role during AM symbiosis. Actually, a reduced mycorrhizal colonization is observed in mutant plants impaired in the brassinoesteroid receptor or in brassinoesteroid biosynthesis [24][25]. Although the role of other plant hormones in mycorrhizal establishment and development has been less studied, it is thought that most of them are involved in these processes. Salicylic acid, ethylene and cytokinins have been reported to have a negative role on AM fungal penetration and colonization [22], while auxins have been observed to positively regulate arbuscule development and functionality [26]. For the jasmonic acid, both positive and negative effects on mycorrhization have been observed [27]. Moreover, as it is well-known, hormones do not act independently, but a complex hormonal dialog regulates plant development and responses. In the case of AM regulation, the antagonistic interactions ABA-ethylene and ABA-giberellin, have been shown to regulate mycorrhizal development and arbuscule formation, respectively [16][28][29].

In addition to the hormonal signals, there is evidence indicating the presence of other essential signalling molecules during mycorrhization. For example, recent insights point to a role of coumarins as novel signals in the pre-symbiotic chemical dialog by promoting fungal metabolism and inducing the initial steps of AM colonization [30]. Another candidate to have a role in pre-symbiotic signalling is a hypothetical compound transported by the plant N-acetylglucosamine exporter NOPE1 [31]. In addition, recent research has shown that the KAI2/D14L and the DLK2 receptors, which are phylogenetically close to the strigolactone receptor D14, play relevant roles in the mycorrhizal symbiosis [32][33], and then it is expected that the not-yet identified corresponding ligands (of plant or fungal origin) might be important in AM signalling and regulation.

Apocarotenoid compounds seem to be especially important in AM regulation [34]. Apart from SLs and ABA, and the possible ligands of D14L and DLK2, other types of apocarotenoid molecules such as zaxinone, cyclohexanone derivatives and mycorrhizadicins are very likely involved in the control of the AM symbiosis [35][36][37][38].

Knowledge about the possible signals from fungal origin involved in the regulation of mycorrhization is very scarce. Due to methodological limitations to perform genetic approaches on AM fungi, it is very difficult to assign specific signalling roles to a particular fungal molecule. At this respect, a combination of two kinds of chitinaceous molecules, commonly known as Myc factors, has been shown to be essential for AM establishment [39]: the Myc-LCOs (lipochitooligosaccharides) and the Myc-COs (short-chain chitin oligomers). AM fungi also secrete proteins, known as "effectors" to communicate with the host plant and to modulate the immune response to allow mycorrhization. Although only SP7, SIS1 and CRN1 have been identified as fungal effectors participating in the establishment of the AM association [40][41][42], it is expected that many other effectors should be involved in AM regulation. Actually, in silico analyses in the genome of *R. proliferus* have predicted the presence of coding regions for 416 small secreted peptides [43]. Also, in the genome of *R. irregularis*, 220 candidate effector genes are present, of which 95% are also found in *R. clarus*.

3. Transcriptional Regulation of Arbuscular Mycorrhizal Symbiosis

A considerable number of studies have shown that large transcriptional changes are induced in the plant host during all stages of colonization. The major portion of regulated genes is involved in signalling, protein metabolism, nutrient transport, secondary metabolite biosynthesis, cell wall modification and lipid metabolism. Furthermore, a significant number of genes encoding putative transcriptional regulators are differentially expressed in mycorrhizal roots, suggesting that AM development is regulated by a complex transcriptional control network [44][45][46][47] in which the GRAS gene family have a prominent role [48] (**Figure 1**).
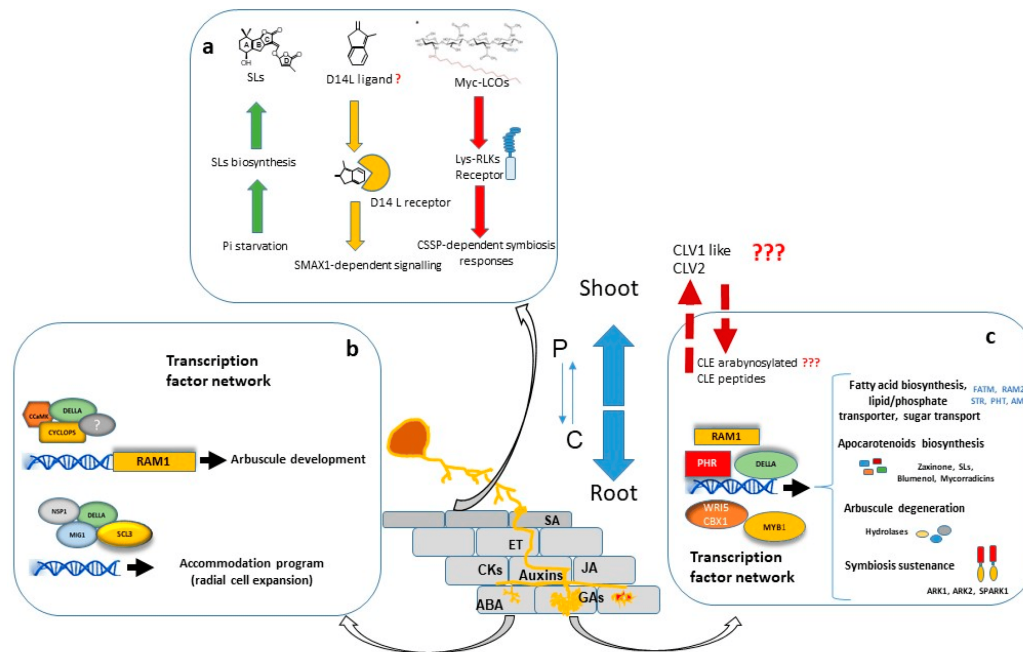
Figure 1. Development of the arbuscular mycorrhizal (AM) symbiosis and its molecular regulation at different stages. AM symbiosis facilitates mutual nutritional benefits: the plant provides carbon (C) to AM fungi in form of carbohydrates and fatty acids, while AM fungi provide minerals, mainly inorganic phosphate (Pi) and nitrogen to the plant. The availability of the different nutrients is a key factor determining the establishment and development of the interaction. AM symbiosis alters plant hormonal homeostasis, and phytohormones play a key regulatory role in the establishment and functioning of the AM symbiosis at different levels: regulating physiology and growth, as well as defense and stress adaptation in AM plants, and participating in the formation and turnover of AM structures. At initial stages (**a**), Strigolactones (SLs), secreted from host roots under Pi starvation, induce fungal spore germination and hyphal branching, facilitating the contact of the fungal hypha with the root and the formation of the hyphopodium. In response to AM perception, a complex of D14L receptor with a yet unknown D14L ligand is proposed to promote the degradation of SMAX1 and the downstream activation of target genes, including symbiosis-related and SL synthesis genes necessary for the accommodation of AM fungi in host cells. AM-released chitinaceous molecules (Myc-LCOs) are proposed to be detected by specific Lys-RLKs with the formation of a receptor complex that leads to the induction of the common symbiosis signaling pathway (CSSP)-dependent symbiosis responses, including transcriptional regulation of AM symbiosis-related genes, which promotes the successful colonization of host root cells by AM fungi. A number of CSSP-activated nuclear transcription factors including CCaMK and CYCLOPS form complexes with a large number of GRAS domain-containing transcription factors, including DELLA, MIG1 and SCL3 that enable the downstream activation of symbiotic genes that facilitate the morphological accommodation of the root cell hosting the fungus, and possibility arbuscule development through the activation of RAM1 (**b**). Arbuscule functionality, maintenance and turnover (**c**) are also dependent on a number of nuclear transcription factors such as PHR, RAM1, DELLA, MYB1 and WRI5A/B that regulate transcriptional programs related to biosynthesis and the transport of nutrients, and biosynthesis of apocarotenoids compounds with regulatory roles. PHRs integrate phosphate starvation signaling, regulating mechanisms for both direct uptake of soil phosphate and AM symbiosis. DELLA and MYB1 regulate arbuscule degradation through activation of genes involved in hydrolysis processes. Receptor Kinase-2 from the subfamily of land plant-specific receptor-like kinases (rice ARK1, ARK2 and SPARK1), has been characterized as having a role in the post-arbuscule formation required for sustaining root colonization. After fungal colonization, root-derived CLE peptides (MtCLE53 and MtCLE33 in *Medicago*) have been proposed as activating signals that trigger a mycorrhizal autoregulation response (AOM) in shoots. The participation of CLV1-like receptors such as SUNN and the hydroxyproline O-arabinosyltransferase RDN1 required for post-translational CLE peptide modification in the AOM signaling process has been proposed.

Transcriptional regulation of symbiotic genes is in part dependent of the Common Symbiosis Signalling Pathway (CSSP) activated during AM and Root Nodulation. Nuclear calcium oscillations generated in plant root cells upon the perception of external symbiotic fungal signals, activate CYCLOPS/IPD3, a primary and central transcription factor of the symbiotic signalling response [49][50]. Among other possible direct target promoters, CYCLOPS in a complex with CCaMK and DELLA, binds the *RAM1* promoter and induces *RAM1* expression [51], which encodes a key transcription factor required for arbuscule development. Part of the Myc-LCO and CO response is dependent on the GRAS protein NSP1 [52][53][54], probably by establishing a regulatory module together with NSP2 and the CYCLOPS-CCaMK-DELLA complex, as suggested by Jin, et al. [55].

Interestingly, recent research has shown that transcriptional regulation of symbiotic genes is not only dependent on the CSSP triggered upon perception of fungal signals and mediated by CYCLOPS/IPD3, but also the phosphate starvation signalling plays a highly relevant role, and the PHR (Phosphate starvation response) TFs govern the regulation of AM-related genes [56]. Moreover, computational analysis carried out by these authors revealed that 42% of the promoter regions of AM-regulated genes in rice carry P1BS (PHR1 Biding Site) motifs, strongly suggesting that Pi starvation plays a central role in the transcriptional activation of a wide range of AM-symbiotic genes.

For arbuscule development, RAM1 is assumed to be the master transcriptional regulator. *RAM1* gene expression is induced by both, Pi starvation conditions through binding of PHR TF to the P1BS element of the *RAM1* promoter [56], and also by the CSSP through binding of CYCLOPS TF to a cis element (AMCYC-RE) of the *RAM1* promoter [51]. Experiments performed in *M. truncatula*, *L. japonicus* and petunia, suggest that RAM1 is essential for the formation of the periarbuscular membrane and for arbuscule branching, and also probably for plant-fungus nutrient exchange [51][57][58][59][60]. The RAM1-dependent activation of several of these symbiotic genes might be mediated by AP2 transcription factors, such as WRI5 or CBX1 [59][61][62].

Arbuscule development requires to be accompanied by cell expansion of cortex cells for accommodation of arbuscules. At this regard, the adjustment of cell size during arbuscule life cycle has been suggested to be regulated by two different modules of GRAS transcription factors with antagonistic actions. In one hand, MIG1 (Mycorrhiza Induced GRAS 1) transcription factor, in a complex with DELLA, promotes radial expansion of arbuscule hosting cells while, in the other hand, MIG2 and SCL3, also in concert with DELLA, restrict cell expansion [63][64].

Arbuscules are continuously being recycled. They have a relatively short life, around 2-3 days, and are rapidly degraded after 2-7 days [65][66]. The quick removal of senescent arbuscules might be a plant regulatory mechanism to restrict the presence of fungal arbuscules that are not providing benefits to the plant. The *M. truncatula* AM-induced gene *MYB1* encodes a transcription factor which, in association with NSP1 and DELLA, has been reported as a key regulatory element required for the induction of many genes associated to arbuscule degeneration, such as cysteine proteases and chitinases [67]. Recent research carried out by Wang, et al. [68] in *M. truncatula*, also shows that the SPX-domain containing proteins SPX1 and SPX3 regulate arbuscule degradation, probably by sensing the delivered Pi at the arbuscule level.

Apart from the transcriptional regulation mediated by TFs, posttranscriptional mechanisms for AM gene expression regulation have been also identified. For example, miRNAs from the miR171 family seem to be involved in maintaining the balance of AM colonization [69][70]. In particular, the microRNA miR171h, which is induced in *M. truncatula* during AM colonization and by Myc-LCOs, has a repressing role on mycorrhizal colonization [69].

4. Systemic Autoregulation of Arbuscular Mycorrhizal Symbiosis

In order to balance the energy cost with the benefit gained, plants employ a systemic negative feedback loop to control the formation of nutrient-acquiring symbioses. This mechanism of feedback control is particularly important in legumes, where existing nodules systemically inhibit subsequent nodulation in other parts of the root system through a process termed "autoregulation of nodulation" (AON) [71]. A similar regulatory mechanism for AM symbiosis has been reported, and the systemic autoregulation of AM colonization (AOM) in split root studies has been observed in both legumes and non-legumes [72][73]. AOM pathway shares some elements with AON, and physiological studies in legumes have indicated there is at least some overlap in the genes and signals that regulate these two symbioses. In addition to its role in nodulation, the CLV1-like protein is also essential in the AOM pathway since *clv1*-like mutants across legume species (*sym29*, *sunn*, *nark*, and *har1*) also display an increased AM fungal colonization, implicating a role for these LRR-RLKs in autoregulation of mycorrhizal symbiosis (revised by Wang, et al. [74]). Recently, first genetic evidence for the AOM pathway in non-legumes has been obtained in tomato. Compared with WT, *clv2* plants displayed a significant increase in AM colonization, including arbuscule frequency, suggesting a role for the tomato CLV2 in AM development [74]. In addition, recent studies provided evidence for a functional role of CLE-mediated signalling in AOM [75][76].

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