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Review

Regulation of protein trafficking: Posttranslational mechanisms and the unexplored transcriptional control

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ABSTRACT

Endomembrane protein trafficking assures protein location through the endocytic and secretory routes. Trafficking pathways are diverse, depending on the proteins being trafficked, the final destination as well as their itinerary. Trafficking pathways are operated by machineries composed of a set of coordinately acting factors that transport proteins between compartments. Different machineries participate in each protein trafficking pathway, providing specificity and accuracy. Changes in the activity and abundance of trafficking proteins regulate protein flux. The preponderance of one pathway over another regulates protein location and relocation. Cellular requirements change during different processes and in response to stimuli; modulation of trafficking mechanisms must relocate proteins or alternatively increase/decrease the targeting rate of certain proteins. Conventionally, protein trafficking modulation has been explained as posttranslational modification of components of the relevant trafficking machinery. However, trafficking components are also transcriptionally regulated and several reports support that this regulation can modulate protein trafficking as well. This transcriptional modulation has an impact on plant physiology, and is a critical and fundamental mechanism. This scenario suggests a determinant mechanism that must be considered in the endomembrane protein trafficking research field.

Contents

Abbreviations: TGN/EE, trans-Golgi network/early endosomes; MVB/PVC, multi-vesicular body/prevacuolar compartment; SNARE, soluble N-ethylmaleimide-sensitive factor adaptor protein receptor; PR, pathogen-related.

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1. Introduction

The physiology of a plant and its ability to respond to environment conditions depend on cellular functioning of the tissues. Since cellular processes occur in compartments within the cell, protein function depends on its suitable cell location. Once proteins are synthesized the proper destination has to be assured in order to maintain cell functioning and fulfill cell requirements. In some cases, proteins are relocated from the resident compartment to another as a constitutive behavior or as part of signaling pathways and regulation mechanisms.

The plant endomembrane system is composed of several membranous compartments that are physically and functionally interconnected through diverse and specific protein trafficking pathways [1,2]. These compartments are the plasma membrane, trans-Golgi network/early endosome (TGN/EE), multivesicular body/prevacuolar compartment (MVB/PVC), vacuole, Golgi apparatus and endoplasmic reticulum (Fig. 1A).

Protein trafficking among endomembrane compartments is diverse, depending on the type of protein being trafficked as well as the machinery involved in its journey. The trafficking pathways within the endomembrane system are broadly classified into secretory and endocytic routes according to the original location of the trafficked proteins (Fig. 1A). *De novo* synthesized proteins traffic to their resident compartment through the secretory route. Proteins previously located in their resident compartment traffic through the endocytic route to a different intracellular compartment. In the latter case the protein may recycle back to the original compartment or else to the vacuole for degradation through the endocytic pathway. The existence of endocytosis in plant was doubted for long time, however it is already probed that clathrin-mediated endocytosis is functional in Arabidopsis [3].

Within the endomembrane system, proteins traffic from a donor compartment to a target/acceptor compartment by means of vesicle/membrane flux as well as compartment maturation, which is driven by vesicle and tubule fusion, across specific and highly regulated pathways [1–5]. Endomembrane protein trafficking are driven by molecular machineries composed of proteins involved in packing the cargo protein into the vesicles, as well as the formation, recognition, tethering, and reception of the vesicle [5]. Active trafficking mechanisms are necessary to assure that newly synthesized proteins reach the resident compartment. Higher efficiency, likely more activity of the trafficking machinery, may be required if the level of synthesis of the delivered protein increases. Therefore the targeting pathways and thus trafficking proteins have to be flexible and efficient. Conversely, if the targeted protein level decreases, trafficking activity may decrease to levels sufficient to sustain cellular requirements.

It is important to consider that in many cases some trafficking proteins participate only in one particular trafficking pathway, giving specificity to the trafficking route. A typical plant cell has the trafficking machinery for the interconnected endomembrane system, allowing protein trafficking from the endoplasmic reticulum to the resident compartment and its relocation to a different compartment according to cell and plant physiological requirements. It is thus pertinent to understand protein trafficking as a dynamic process in which the machineries for a variety of trafficking pathways coexist. The direction of the cargo protein trafficking and location depend on the balance of all the different pathways affecting their movement. The equilibrium of different trafficking pathways will determine the amount of protein in each compartment. The capacity of changing the equilibrium may be useful when the presence or enrichment of certain protein changes in a particular compartment in response to a stimulus or perturbation. The protein level of trafficking machineries has been shown to be regulated at transcriptional under biotic and abiotic challenges. The equilibrium has to be reestablished to normality after plant recovery. Therefore transcriptional modulation of protein trafficking should be transitory and highly regulated.

Protein trafficking should be a highly regulated process allowing fine-tuned modulation according to plant cellular and physiological requirements. Trafficking coordination is more noticeable in the cases of a plasma membrane resident proteins that are internalized by endocytosis. The plasma membrane proteins are synthesized in the endoplasmic reticulum and then are trafficked to their resident compartment, the plasma membrane. These proteins are internalized to TGN/EE by endocytosis upon a particular stimulus. From the TGN/EE the proteins can either recycle back to plasma membrane

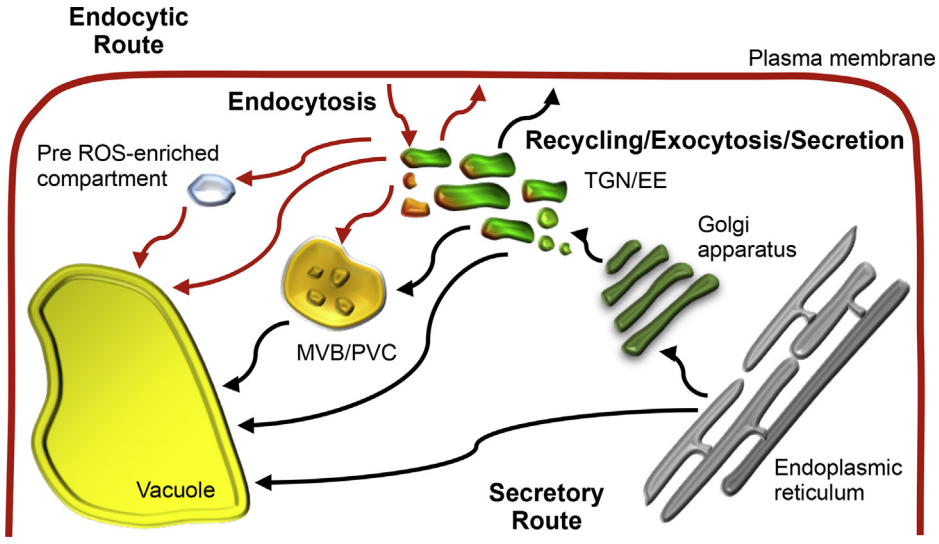

Fig. 1. Plant endomembrane protein trafficking pathways. Endomembrane system trafficking pathways transport proteins along its compartments; the plasma membrane, the Trans-Golgi/Early Endosome (TGN/EE), the Multivesicular Body/PreVacuolar Compartment (MVB/PVC), the vacuole, Golgi apparatus, endoplasmic reticulum and the putative Pre-ROS-enriched compartment. Endocytic and secretory trafficking pathways are represented by red and black lines, respectively. The endocytic route includes all protein trafficking pathways involved in protein relocation from the plasma membrane to intracellular compartments including TGN/EE, MVB/PVC and vacuole, which is defined as endocytosis, as well as, from those compartments back to the plasma membrane by recycling pathways. The secretory route includes the pathways involved in targeting *de novo* synthesized proteins from the endoplasmic reticulum to their resident compartments (black lines).

or alternatively they may travel to the vacuole [2,4]. Therefore, for these proteins there are at least three or four different pathways regulating their trafficking through the endomembrane system, and the ratio in which they are located in each compartment. This regulation compromises several trafficking machinery proteins. This simple case highlights the complexity and highly coordinated trafficking pathway.

Protein trafficking depends on the abundance and activity of the trafficking machinery present in the cell, as well as on the balance among the different pathways. It is a highly regulated process modulated at transcriptional and posttranslational levels, according to the cell status and requirements. Endomembrane protein trafficking and its regulation are integrative and complex processes that are crucial to plant cell and physiology. In this review, the regulation of protein trafficking during physiological processes and its implications in hormone transport, biotic and abiotic stress responses are considered. The transcriptional regulation of endomembrane protein trafficking is discussed as a critical and fundamental modulation mechanism.

2. Protein trafficking: effectors and modulators

The trafficking machinery works specifically, accurately and efficiently, delivering proteins from one compartment to another. Among these, small GTPases, soluble N-ethylmaleimide-sensitive factor adaptor protein receptor (SNARE) proteins, phosphatidylinositol-kinases and phosphatidylinositol-phosphatases, and cargo receptors are the main players in protein trafficking [5]. In the following part the main proteins involved in modulation of protein trafficking in terms of flux and the trafficking pathway balance/imbalance will be briefly described.

2.1. Small GTPases: active and inactive states determine protein trafficking

Small GTPases play a key role activating trafficking pathways, interacting and recruiting trafficking machinery (Fig. 2A). Their activity and abundance determine flux through a trafficking pathway. The small GTPases are monomeric GTP-binding proteins that act as regulatory switches depending on their conformation, which is determined by whether the nucleotide GTP or GDP is bound to their structure. They cycle from an inactive state, the GDP-bound isoform, which is its constitutive state, to the active state as the GTP-bound isoform. The GTP-bound isoform executes the function by activating a downstream effector or recruiting proteins to trigger a particular process [6]. The small GTPases are regulated by guanine nucleotide-exchange factors and GTPase-activating proteins. The guanine nucleotide-exchange factor induces the exchange of GDP for GTP, achieving the active state by a conformational change that allows the interaction of the small GTPase with membranes and proteins [6]. The inactivation of the small GTPase is performed by the GTPase-activating protein that activates the small GTPase hydrolytic activity, leading to the hydrolysis of GTP to GDP [6].

Two main types of the RAS superfamily of monomeric GTP-binding proteins are part of protein trafficking machinery: Sar/Arf small GTPases, which are involved in vesicle formation and budding, and small Rab GTPases, involved in vesicle recognition, docking and fusion [6–8]. A large diversity of these types of proteins has been described in Arabidopsis [7,8]. They are associated with different endomembrane compartments and trafficking pathways, giving specificity for a certain pathway [7,8]. Sar/Arf and Rab small GTPases, through a GTP- or GDP-bound state, determine the capability of effector recruitment and interactions with specific endomembrane compartments, allowing protein trafficking function [6,7].

2.2. SNARE proteins: fusion mechanism determining target specificity

It is difficult to picture how vesicle formation, trafficking and fusion operate and maintain accuracy and specificity, due to the numerous and diverse endomembrane trafficking pathways. SNARE proteins are the key players in vesicle fusion; their role involves vesicle docking to the specific acceptor compartment. SNAREs are classified according to their location and function into v-SNAREs and t-SNAREs, which are located in the membrane of the vesicle or the target compartment, respectively. v-SNAREs are packaged in the vesicle during vesicle formation in the donor compartment through interaction or assembly with vesicle coat proteins [4,5]. The v-SNAREs, with assistance of tethering factors and Rab small GTPases, interact with several, usually two or three, t-SNAREs located exclusively in the acceptor compartment [9,10]. The interaction of v-SNAREs with specific t-SNAREs ensures accuracy and specificity of protein targeting [9,10]. This interaction establishes a tight protein complex that allows fusion of the two membranes, delivering the cargo protein carried by the vesicle to the target compartment (Fig. 2B) [5,10]. The v-SNARE/t-SNARE complex disassembles after the membrane fusion occurs and the SNAREs are then available for the next round of trafficking [5,10]. Hetero-oligomeric interactions and formation of the v-SNARE/t-SNARE complex are essential for vesicle recognition and fusion with the suitable acceptor compartment [9,10]. A given vesicle fuses only with a target compartment due to the specificity of the interaction between v-SNAREs and t-SNAREs. Therefore the accurate transport through a trafficking pathway requires and depends on the abundance of SNAREs and their availability to interact with their partners, which modulates the trafficking pathway dynamics.

2.3. Membrane composition and phosphatidylinositols. A dynamic modulation

Since protein trafficking requires membrane for vesicle formation it is expected that membrane composition will play a role in protein trafficking [11]. The phosphatidylinositol phosphorylation state is an important membrane property. This state is determined by phosphatidylinositol kinases and phosphatases [12]. Trafficking proteins such as Rab GTPases, Epsins, retromer and ESCRT proteins that contain the FYVE and ANTH domains are able to interact with the lipids phosphatidylinositol 3-phosphate and phosphatidylinositol 4,5-bis phosphate [13]. These interactions allow the recruitment and attachment of such soluble proteins to specific subcellular membranes therefore the spatiotemporal regulation of phosphatidylinositol phosphorylation state is relevant for protein trafficking (Fig. 2C) [13,14]. The phosphatidylinositol phosphorylation state depends on the catalytic activity of phosphatidylinositol-kinases/phosphatases that are activated or inactivated in specific cell conditions or in response to stimuli [12]. Consequently, inhibition of phosphatidylinositol 3-phosphate kinase or phosphatidylinositol 4,5-biphosphate phosphatase provokes impaired trafficking, leading to physiological alteration related to this disturbance [14–16]. The evidence indicates that the phosphatidylinositol phosphorylation state is a dynamic and important point in protein trafficking modulation. The membrane sub-compartmentation in lipid rafts is another important membrane property to consider. Lipid rafts have a role in membrane organization, allowing recruitment of trafficking proteins, membrane domain formation and membrane curvature, as has been described in eukaryotic models (Fig. 2C) [17].

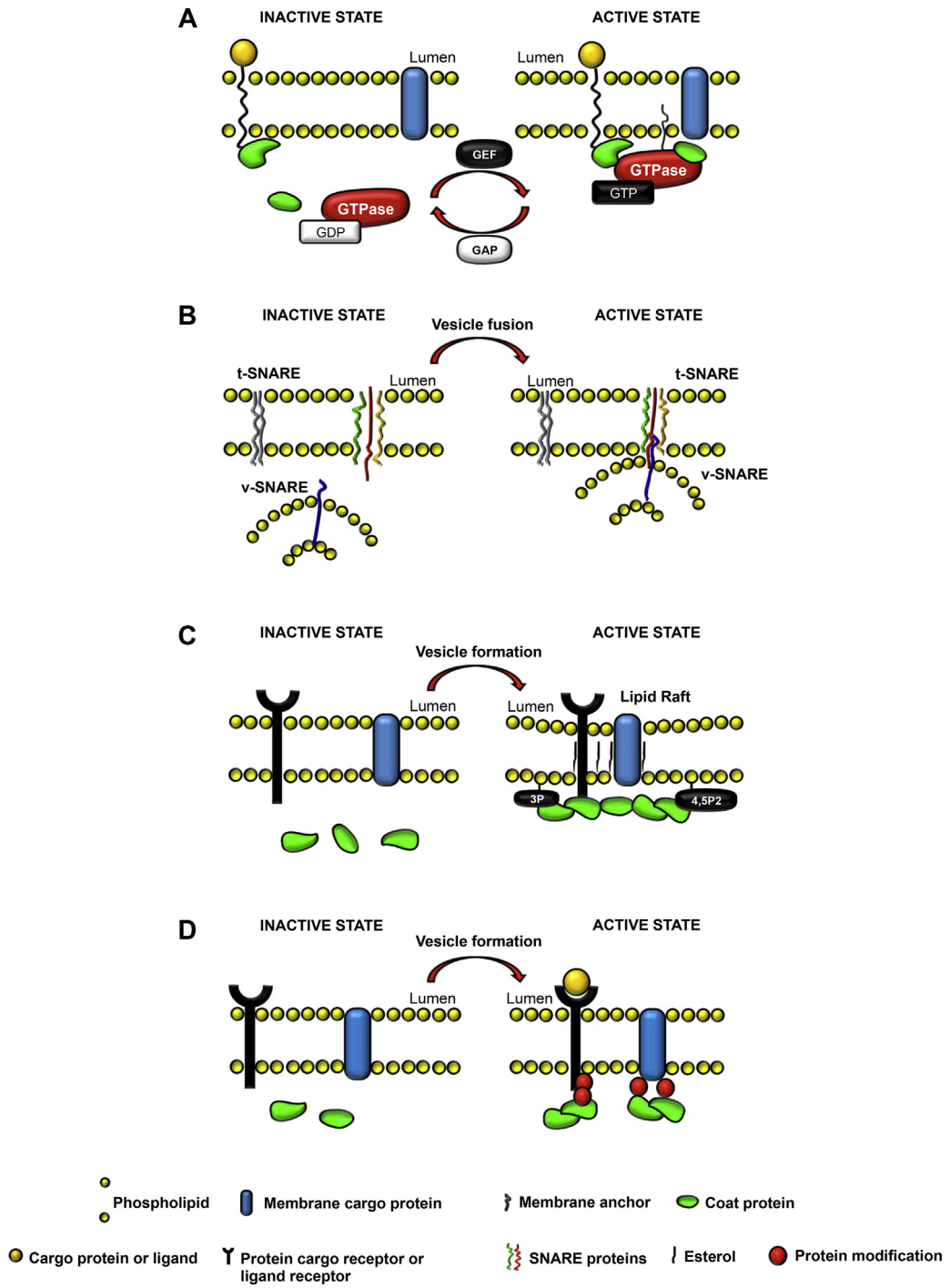

Fig. 2. Effectors and modulators of protein trafficking mechanisms. (A) Small GTPases are constantly switching from the active to the inactive state. Arf/Sar1 and RabGTPases switch from an inactive state (GDP bound) to an active state (GTP bound). The nucleotide exchange is induced by guanine nucleotide-exchange factor (GEF). The active small GTPase isoform interacts with the lipids of the membrane and recruits several trafficking components leading vesicle formation in the case of Arf/Sar1 GTPases and recognition of vesicle identity and membranes fusion for Rab GTPases. The small GTPases are inactivated by hydrolyzing GTP to GDP, process induced by a GTPase-activating protein (GAP). The inactive small GTPase ceases the interaction with trafficking components, membrane and proteins. Small GTPases follow the cycle of activation and inactivation many times. (B) SNARE proteins facilitate specific vesicle recognition and fusion. v-SNAREs are membrane proteins located at the vesicle and t-SNARE are located at the acceptor compartment. The v-SNARE interacts specifically with a given set of t-SNAREs (two or three) establishing a tight protein complex that allows the fusion of the two membranes, vesicle and compartment membrane. The compatibility of the SNAREs determines membrane fusion specificity. The raised level of a determinate set of SNAREs will increase the chance of membrane fusion at the target compartment (C) Membrane lipid composition plays a role in recruiting trafficking machinery. Trafficking components interact with the lipids phosphatidylinositol 3-phosphate (3P) and phosphatidylinositol 4,5-bisphosphate (4,5P2), facilitating the recruitment of proteins involved in vesicle formation. Phosphorylation state of phosphatidylinositols in the membrane is determined by the activity of phosphatidylinositol kinases and phosphatases. Trafficking components are recruited when phosphoinositol 3-phosphate and phosphoinositol 4,5-biphosphate are present in the membrane (active state). Phosphatidylinositol state is dynamically cycling from phosphorylated to unphosphorylated state and, therefore, from active to inactive state of trafficking. Additionally, lipid rafts assist the recruitment of trafficking components into specific membrane domains, facilitating this process. (D) The cargo protein receptor is activated for its trafficking. Soluble cargo proteins are recognized by a transmembrane receptor that chaperons them along the trafficking pathway. Membrane cargo proteins may work as their own receptors. The interaction with the cargo or a ligand induces conformational changes leading induction of protein trafficking. Furthermore, this interaction can induce posttranslational modifications of the receptor. Cargo protein receptor and transmembrane cargoes can be ubiquitinated or phosphorylated (active state) leading recruitment of trafficking components for further protein targeting and relocation.

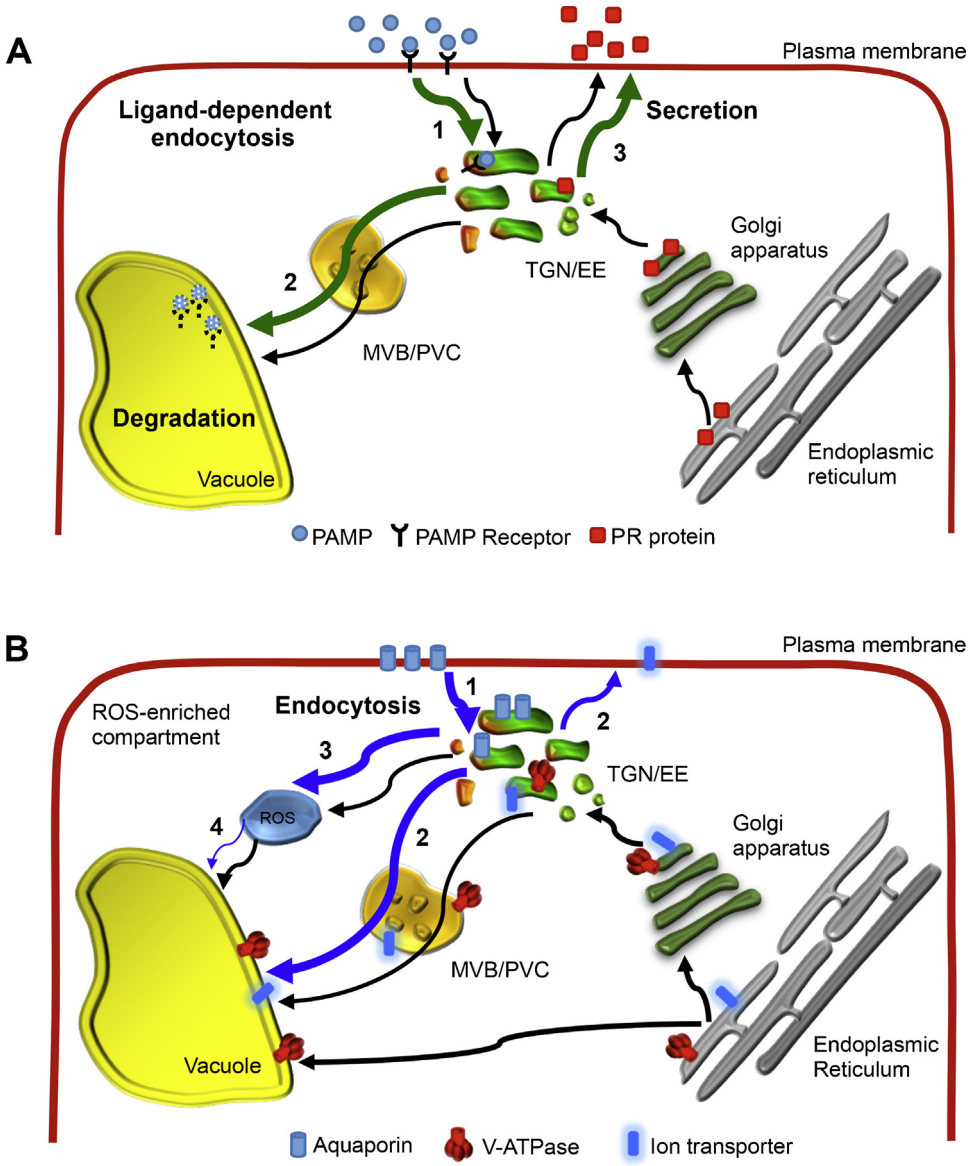

Fig. 3. Modulation of endomembrane trafficking pathways. (A) Protein endocytic trafficking is induced in response to pathogen attack. The ligand pathogen-associated molecular pattern (PAMP) induces endocytosis of its plasma membrane receptor (1). The receptor trafficking toward the vacuole for degradation is a mechanism of signal attenuation (2). Secretion is activated to increase the trafficking of the Pathogen Related (PR) Protein to the apoplast (3). Constitutive trafficking pathways are shown using black arrows while green arrows show regulated trafficking pathways. Arrow thickness correlates with the trafficking rate through the corresponding trafficking pathway compared to the regular condition (B) Trafficking mechanisms are modulated under abiotic stress. The water channel aquaporins are transiently arrested at the TGN/EE after induction of their endocytosis (1). Protein trafficking to the vacuole and plasma membrane are also needed to deliver or relocate proteins such as ion transports and v-ATPases, regulating in such a way ion homeostasis (2). Additionally, Pre-ROS-enriched compartment becomes a ROS-enriched compartment most likely for induction of protein trafficking associated to TGN/EE (3). ROS compartmentation and inhibition of ROS trafficking to the vacuole would minimize the oxidative burst (4). Constitutive trafficking pathways are shown in black arrow, while regulated trafficking pathways are shown in blue arrows. Arrow thickness correlates with the normal trafficking rate of the pathway.

2.4. Cargo receptor and coat proteins. Driving proteins into vesicles

Protein trafficking depends on cargo receptor proteins that act as chaperones, driving the cargo to a specific compartment. In the case of a soluble protein recently synthesized on the endoplasmic reticulum or being relocated from a particular compartment, a receptor protein is required for targeting (Fig. 2D). Cargo membrane proteins may act as receptors in this process. The cytosolic portion of the cargo receptor or the cargo membrane protein interacts with specific trafficking proteins, allowing the packaging of cargo protein into an incipient vesicle to be further delivered to another compartment (Fig. 2D) [18]. The vesicle formation process occurs through sequential and hierarchical interactions between cargo receptor or cargo membrane protein and vesicle coat proteins [3,6,18]. The most important vesicle coat proteins are clathrin, COPI and COPII. These three types of protein complexes interact with different sets of adapter proteins and small GTPases to generate a new vesicle [3,5].

Cargo receptors/cargo membrane proteins are modified by ubiquitination or phosphorylation that can induce their protein recruitment capability and trafficking (Fig. 2D). This kind of modification occurs in several plasma membrane receptors that are relocated to TGN/EE or MVB/PVC through endocytosis [19,20]. However, protein trafficking modulation mediated by conformational changes in the cargo receptor also occurs in other

compartments of the endomembrane system. Posttranslational modifications have to be removed for further trafficking depending on cell location of the cargo receptor. Moreover, the protein recruitment capability of the cargo receptor/cargo membrane protein could be modulated by interaction with accessory proteins and ligand interaction [20,21]. The Unfolded Protein Response sensor/transducer bZIP28 is retained in endoplasmic reticulum bound to luminal chaperone protein BIP as its ligand. BIP is released from the complex in response to the overloading of the endoplasmic reticulum with unfolded proteins, leading to bZIP28 relocation to the Golgi apparatus where bZIP28 signaling is activated [22].

3. Plant protein trafficking modulation: when and where

Endomembrane protein trafficking targets proteins accurately, based on the activity and turnover of the protein trafficking machinery. Protein trafficking has been proven to be essential for plant physiology and has an active role in processes such as cell division, hormone transport and signaling, and consequently in different developmental processes during plant life [1,23]. Furthermore, it plays an important role in physiological responses to stress and environmental stimuli such as light, gravity, and pathogen attack [24,25]. Since all these processes occur in a spatio-temporal determinated manner, a particular pathway must be modulated transiently and then returned to the initial steady state condition.

In cell division and particularly during cytokinesis there is a need for concerted trafficking of membrane components from the TGN/EE which forms the cell plate [22]. In the last phase of cell division, protein, membrane and cell wall components must be targeted for the cell plate to be built at the division edge [26]. This process occurs in a very precise stage of the cell cycle, therefore the particular trafficking pathway to the cell plate has to be activated at this specific time window and later shut off.

Auxin flux is another example of trafficking regulation and its relevance to plant physiology. Auxin transport is mainly regulated by plasma membrane auxin efflux transporters, PIN proteins, are polarly located pointing toward the auxin efflux direction [23]. PINs constitutively travel back and forth from plasma membrane to the TGN/EE by clathrin-mediated endocytosis [3,23]. The plasma membrane location of PIN proteins is accomplished by the equilibrium of two endomembrane trafficking pathways: endocytosis from the plasma membrane to TGN/EE and then recycling back to the plasma membrane [24]. Therefore, modulation of this equilibrium leads to an increase/decrease of PINs in the plasma membrane, inducing a change in auxin concentration and consequently a physiological response [23,24]. This modulation may take place, for example, during gravitropic response. An auxin gradient dependent on PIN relocation is induced in response to gravistimulation, leading to primary root re-orientation [24]. The trafficking pathway from plasma membrane to the vacuole is predominant in the cells on the upper side of the gravistimulated root, while cells on the lower side maintain PINs in the plasma membrane, leading to an auxin gradient and thus to root growth and curvature in response to gravistimulation [24]. During embryo, leaf and root development auxin transporters are polarly located at the plasma membrane, depending on the tissue and its context [23]. The apical and basal plasma membrane distribution and their changes depend on trafficking regulation, since several trafficking component loss of function mutants result in impaired location auxin efflux and auxin-related phenotypes [23].

Protein trafficking regulation is fundamental for the response to environmental stimuli, including biotic and abiotic stress. An endocytosis pathway of the plant receptor is induced during pathogen infection [27,28]. This endocytosis-dependent mechanism is activated by the interaction between the receptor and its ligand; for example under pathogen infection the receptors LeEIX2 and FLS2 bind to their ligands EIX and flagellin, that are present in a variety of fungi and bacteria, respectively [27,28]. The ligand-triggered internalization of the ligand-receptor complex leads to pathogen response signaling activation [25,29]. The secretory pathway is also induced under infection and secretes Pathogen-related (PR) proteins by exocytosis toward the infection site, conferring resistance [25,29]. Protein trafficking must be efficient and fast in sensing the pathogen and establishing a response against it. The modulation of endocytosis is more likely predominant over other pathways as soon as the pathogen attacks. However, protein secretion is predominant in the trafficking balance after signaling occurs (Fig. 1B). An analogous protein trafficking modulation is required for a successful symbiotic interaction between plants and microorganisms [30].

Several processes take place during abiotic stress which imbalance cell function, particularly high salinity and drought. Homeostasis is reestablished in part by reducing the water loss from the cell, inducing Reactive Oxygen Species (ROS) detoxification and readjustment of ion concentration. Protein trafficking has a relevant role by relocating the water channel aquaporins from plasma membrane to TGN/EE, diminishing water loss [31]. There is an increase of ROS accumulation under abiotic stress in small compartments located all over the cell [32,33]. The identity of these compartments is still unclear, however they most likely correspond to TGN/EE [33]. In any case, the formation of these compartments implies transport of ROS from the cytoplasm into the membrane compartments or trafficking of ROS-generating enzymes to them. In both cases, trafficking mechanisms would be required for targeting the ROS transporters or enzymes as well as the membrane of the compartments. Reestablishing ion homeostasis after salt stress, for instance, require re-targeting of membrane proteins such as ion channels and transporters. This targeting is important for proteins located in the vacuole such as ion transporters and V-type H^+-ATPase, because ions are accumulated in this compartment [34]. Therefore, protein trafficking has an important and active role in abiotic stress response, ensuring restoration of homeostasis in at least three essential aspects: water availability, ROS stress and ion homeostasis (Fig. 1C).

The diverse protein trafficking pathways within the endomembrane system depend on the trafficking mechanisms responsible for vesicle formation and transport, and on the balance between different trafficking pathways. Many types of trafficking proteins are recruited and activated during the regulation of protein trafficking (Section 2), determining compartment identity, the trafficking pathway specificity and ensuring protein targeting and relocation [6–10]. As discussed above (Section 1), the activity of the trafficking machinery is regulated, allowing modulation of a particular pathway in response to developmental and environmental signals. Protein trafficking regulation has been described typically as a posttranslational process in which components of trafficking mechanisms are activated/inactivated which increase/decrease protein trafficking through the pathway. Nevertheless, new evidence indicates transcriptional regulation as another important level of control that leads to changes in protein trafficking, both in quantity and composition.

4. Protein trafficking regulation: a conventional view

As mentioned above (Section 2.1), the function of small GTPases is modulated through a balance between active/inactive states, allowing them to execute protein trafficking. Protein activation promotes specific interactions with downstream effectors, protein recruitment and by this means protein trafficking flux.

Accordingly, Nevershed Arf-GTPase-activating protein has been implicated in the regulation of trafficking from TGN/EE due to its effect on Arf activity regulation [35]. As expected, loss of function of this Arf-GTPase-activating protein impairs secretion and generates developmental abnormalities in leaves and fruits [35]. Furthermore, the Rab GTPase ARA6 and its Rab-guanine nucleotide-exchange factor, VPS9a, are involved in modulating the endocytic route, working with different SNARE complex assemblies [36,37]. This protein trafficking modulation is implicated in the abiotic response, because constitutive-active ARA6 isoform overexpression confers salt resistance in Arabidopsis, probably by induction of trafficking to the vacuole [37]. Similarly, the Rab GTPases Rab11 and Rab7 also participate in the endocytic route toward the vacuole, since overexpression of these Rab GTPases decreases abiotic stress sensitivity [38]. Additionally, several SNARE proteins have been related to endocytic route modulation in abiotic stress, including the t-SNAREs SYP61, SYP121 and SYP41, and the v-SNARE VAMP711 [31,33,39,40]. The precise cargo proteins that are trafficked by the pathways modulated by these SNAREs in salt stress are still unclear. They could be participating in trafficking modulation of aquaporin location, inducing ion transporter trafficking to the vacuole and leading to ROS compartmentation in membrane organelles, which are important events in abiotic resistance [31–33,37–41] (Fig. 1C). These cases exemplify how small GTPases and SNAREs participate in trafficking regulation during plant development and in response to a physiological stimulus.

The pathogen-associated molecular pattern receptor is internalized by endocytosis activated by ligand interaction during pathogen infection. This receptor is relocated to the vacuole after internalization, where it is degraded as a desensitization mechanism (Fig. 1B) [21,27]. At the same time secretion mediated by the SNARE proteins SNAP33 and VAMP72 is activated [42,43]. The internalization of the pathogen-associated molecular pattern receptor signals downstream both posttranslational modifications and activation of gene transcription [29]. However, whether signaling also induces an increase of the secretion pathway by activation of SNAP33 and VAMP72 remains to be determined.

Protein trafficking is regulated at multiple steps. Cargo selection into vesicles is fundamental for activation of a particular protein trafficking. Vesicle formation, docking and fusion can also be modulated by trafficking mechanisms as discussed above (Section 2). It is quite clear that regulation of trafficking has an effect on plant cell physiology. However, the mechanism by which this modulation takes place is still incompletely understood. In the following section antecedents are presented to depict how transcriptional regulation in trafficking modulation may be involved, as well, its implications for plant physiological processes.

5. Protein trafficking regulation: opening the transcriptional avenue

In addition to the balance between activation and inactivation of trafficking mechanisms, protein trafficking regulation also depends on the abundance of trafficking components. Regulation of trafficking molecular component expression may be decisive for modulating trafficking pathways. Although a cell may have available the molecular machinery for all the trafficking pathways, activation of the endogenous mechanisms may not be enough for cell needs under an exceptional requirement. How is this system able to deliver correctly a large amount of protein? Is posttranslational modulation of the trafficking mechanism enough? It takes a certain amount of time for trafficking mechanisms to deliver a protein and be available for the next round, thus posttranslational regulation may not fulfill all the cell requirements. Could increases in the level of trafficking proteins change the rate of protein trafficking in response to a challenge? During the last decade it has been reported that genes encoding trafficking mechanism components are transcriptionally regulated. In humans TFEB transcription factor coordinately regulates the transcription of these trafficking machinery genes and lysosomal genes, leading to regulation of lysosomal biogenesis [44]. In this case, TFEB regulates trafficking to the lysosome through changes in the expression of genes encoding proteins involved in trafficking [44]. This evidence raises the question whether such regulation may be present in plant endomembrane protein trafficking. This is highly relevant, considering that such gene expression determines trafficking mechanism protein bioavailability and therefore may have an effect on protein trafficking.

The concentration of the vesicle coat protein clathrin determines the endocytic rate of plasma membrane receptor mediated endocytosis in mammalian cells [45]. Therefore clathrin availability is an important regulator of endocytosis dynamics that can be regulated by the rate of transcription [45]. Additionally, the Arabidopsis plasma membrane t-SNARE *SYP121* is down-regulated by dark treatment and up-regulated by light [46]. Oppositely, the expression of t-SNARE *SYP122*, the closest ortholog to SYP121, is induced in darkness [46]. The expression induction of both t-SNAREs correlates with an enhancement of the interaction with their v-SNARE partners, VAMP722 and VAMP721, at the plasma membrane strongly suggesting that vesicle fusion is also increased [46]. Therefore the transcription of SNAREs can be differentially modulated having an impact on protein trafficking (Fig. 4). Whether SYP121 and SYP122 are involved on the same process at the plasma membrane is still unknown. Since they interact with different v-SNAREs most likely they are part of machineries involved on distinct processes. Light-dependent trafficking pathways have been described in Arabidopsis. PIN proteins are relocated from plasma membrane to the vacuole in darkness while light promotes their plasma membrane location (Fig. 4) [47].

Perturbation of Arabidopsis endomembrane trafficking pathways by means of chemical treatments causes changes in the protein level of the trafficking mechanisms [48,49]. These changes are likely due to transcriptional regulation, however effects on protein synthesis or turnover can not be ruled out. The protein level of the trans-Golgi located small GTPase RabA1d decreases following vacuole trafficking inhibition mediated by wortmannin, a specific inhibitor of phosphatidylinositol kinases [48]. In the same conditions the phosphatidylinositol transfer-like protein, Sec14, level also increases [48]. Brefeldin A is a different protein trafficking-altering drug; it inhibits trafficking from the Golgi apparatus to endoplasmic reticulum and also the exocytosis from the TGN/EE compartment to the plasma membrane. Brefeldin A treatment induces changes at the protein level of a vacuolar H-ATPase and cytoskeleton-remodeling proteins that are closely related to protein trafficking [49]. This shows that the system is able to respond to perturbation of trafficking pathways by adjusting protein content, probably due to modulation at the transcriptional level.

The transcription level of trafficking mechanism genes changes in response to many stimuli and processes that require trafficking modulation. The hormone ABA induces accumulation of ROS in subcellular compartments during abiotic stress in Arabidopsis, probably *via* TGN/EE, which fuses with the vacuole [32,33]. A mutant deficient in *VAMP711*, a tonoplast v-SNARE, has decreased levels of ROS in the vacuole, presumably by suppressing trafficking to the vacuole from the ROS-enriched compartment, leading to greater abiotic stress resistance [32,33]. Consistently, the *VAMP711* transcript level is strongly decreased following salt stress and drought treatments in wild type Arabidopsis [32,33]. Probably, under stress conditions due to *VAMP711* loss of function the ROS-containing compartments are not able to fuse with the vacuole, therefore avoiding the vacuolar damage provoked by ROS, resulting

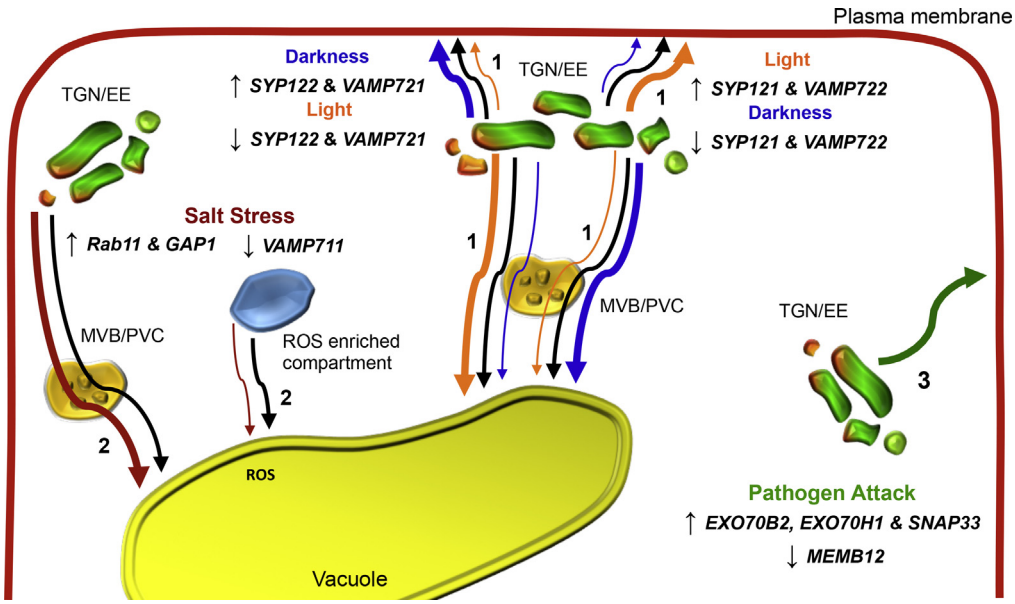

Fig. 4. Transcriptional regulation of trafficking pathways. Plant small GTPases are transcriptional regulated depending on light conditions. The partners *SYP122/VAMP721* and *SYP122/VAMP722* expression is up-regulated (↑) and down-regulated (↓), respectively. The expression of these trafficking genes is opposite in plants grown in darkness. The change on the expression levels most likely leads to a change on the rate of vesicle trafficking between plasma membrane and endosomes. Modulation provoked by light exposure is shown with blue arrows; orange arrows highlight transcriptional modulation in dark-grown plants (1). Under salt stress the *VAMP711*, *Rab11* and *GAP1* small GTPases are transcriptional regulated. This modulation would affect trafficking pathways to the vacuole; inducing the trafficking through endosomes and PVC and inhibiting trafficking of components from the ROS-enriched compartment (red arrows, 2). Transcriptional regulation should afford the trafficking of new cargoes that need to be delivered under certain stimulus. The secretion of PR proteins is activated when the plant is challenged with a pathogen. In response to this attack, *EXO70B2*, *EXO70H1*, *SNAP33* and *MEMB12* are transcriptionally regulated presumably to accomplish the delivery of the newly synthesized PR proteins (green arrow, 3). For all the conditions arrow thickness correlates with the trafficking rate through trafficking pathways compared to the regular growth conditions (black arrows).

in resistance to salt and drought stress (Fig. 4) [32,33]. These results indicate that the abiotic stress response to salt and drought depends on down-regulation of *VAMP711*, supporting the relevance of transcriptional regulation of protein trafficking functioning, although this remains to be proven. Transcriptional regulation under salt stress has been also detected for genes encoding Epsin proteins which are important for the establishment of vesicle curvature. The Arabidopsis Epsin *EHD1* is induced seven-fold above its normal levels by salt treatment, which correlates with greater salt resistance of *EHD1* overexpression lines [50]. Furthermore, the expression of the RabGTPase *OsRab11* and the Arf GTPase-activating protein *OsGAP1* in rice are both induced by salt stress, leading to trafficking to MVB/PVC and/or the vacuole [41]. Interestingly, induction of the expression of *OsRab11* and *OsGAP1* results in a higher trafficking rate toward the vacuole and confers abiotic resistance (Fig. 4) [41]. Abiotic resistance is conferred by down-regulating trafficking component genes such as VAMP711 as well as up-regulating *OsRab11* and *OsGAP1*. These changes in regulation would be explained by the presence of two different TGN/EE-like compartments during abiotic stress, the ROS-enriched compartments and the regular TGN/EE compartments (Fig. 4). VAMP711 would be part of the trafficking machinery for the ROS-enriched compartment, thus reducing its expression would reduce ROS trafficking to the vacuole, conferring abiotic resistance. Rab11 and GAP1 would be components of TGN/EE trafficking mechanism in which their increase in expression would increase trafficking of any protein needed in the vacuole for the abiotic stress resistance (Fig. 4). Overall, this shows that the relationship between abiotic stress response and trafficking to the vacuole may be mediated, at least in part, by transcriptional regulation of the trafficking mechanisms.

The rapid and precise cellular plant response in the exocytosis and secretion pathways is fundamental for establishing a proper defense response to pathogens [25,29]. PR proteins are secreted in response to infection, conferring plant resistance [25]. Endomembrane protein trafficking transcriptional regulation may also have an important role regarding plant biotic stress. In this context, *Exo70B2* and *Exo70H1* expression is induced during pathogen response (Fig. 4). This is consistent with the fact that their loss of function confers pathogen sensitivity [51]. Although Exo70 proteins are involved in exocytosis, their molecular mechanism in this trafficking route and their specific role in pathogen response are not completely understood. Furthermore, the expression of the exocytosis-involved t-SNARE *SNAP33* gene is induced in Arabidopsis during pathogen response [42]. Infection with *Pseudomonas syringae* triggers *SNAP33* expression, leading to the enhancement of PR protein secretion (Fig. 4) [42]. The regulation of protein trafficking also is mediated by a miRNA, highlighting a posttranscriptional mechanism that modulates protein trafficking. The down-regulation of the SNARE *Memb12* during pathogen response in Arabidopsis depends on miRNA393* [52]. *Memb12* down-regulation results in an increase of PR protein exocytosis and consequently increasing pathogen resistance (Fig. 4) [52]. The fine and fast tuning of secretion and particularly exocytosis are essential for plant survival, demonstrating their importance as a cellular process in the plant pathogen response and resistance. Understanding the molecular mechanism for this physiological challenge at the cellular level is fundamentally relevant, and eventually useful for translating the knowledge to applied science.

Both organisms involved in a symbiotic interaction suffer some changes more likely to contribute to and adjust their relationship. Models for plant and bacteria interaction have been described, such as *Medicago truncatula* and *Sinorhizobium meliloti*. The expression of the SNARE *VAMP721a* is directly regulated by "Regulator of Symbiosome Differentiation", a member of the Cysteine-2/Histidine-2 (C2H2) transcription factor family in *Medicago truncatula*, during symbiosome establishment [53]. Another example of transcriptional regulation of trafficking mechanisms is the induction of *LjVTI12* expression, which encodes a SNARE protein, in the mycorrhizal fungus and *Lotus japonica* symbiotic interaction. *LjVTI12* expression is probably induced through CTTC and P1BS cys-regulatory elements

that are involved in mycorrhiza-specific gene regulation [54]. The participation of VAMP721a and LjVTI12 in protein trafficking and symbiotic interactions may be revealed in the future.

It is also interesting that tissue-specific expression confers different properties to endomembrane system compartments, given compartment identity and therefore functional identity in different tissues. This fact may explain why the expression of many *Exo70* subunits genes is tissue-specific, suggesting functional specificity. For example *Exo70a* is expressed in vascular tissue and is involved in tracheal element development, whereas *Exo70C1* is expressed mainly in pollen [55,56]. Similarly, the expression of small GTPase and SNARE genes is also tissue-specific [7,57]. The tissue-specific expression may be understood as a functional differentiation between the pathways involved in and activated by different trafficking proteins expressed in a particular tissue. This is illustrated by the differential sensitivity of different tissues to compounds that inhibit trafficking pathways [58].

The evidence presented strongly suggests that transcriptional regulation of trafficking mechanism components is involved in modulating protein trafficking, leading to changes in the balance of protein trafficking in response to changes in cellular requirements, which would be induced by a stimulus.

6. Perspectives, open questions and challenges

Several cases of modulation of protein trafficking have been discussed. Targeting and redirecting protein cargo and membrane components are constitutive processes; however, under certain conditions cell needs require particular pathways to be predominant. Therefore, modulation of trafficking may increase protein trafficking toward a particular compartment, inducing more protein cargo to reach the desired compartment. Trafficking regulation occurs for proteins involved in fundamental cellular processes as well as in responses to environmental stimuli. The plasticity of endomembrane protein trafficking has a biological advantage; therefore the mechanisms of modulation are critical and crucial to assure accurate behavior.

The modulation of endomembrane protein trafficking has conventionally been considered to be through posttranslational mechanisms in which activation and inactivation of protein activity is the unique mechanism. Undoubtedly, the posttranslational regulation of trafficking in many protein trafficking processes is relevant and suitable for rapid response to new requirements. Nevertheless, new evidence reveals that transcriptional regulation also occurs. Transcriptional regulation could be decisive for supporting and maintaining protein trafficking response especially for extended time periods. Thus, it would be fascinating to identify transcriptional regulators involved in the modulation of trafficking. There is a small number of transcription factors that affect the transcription of single genes encoding trafficking machinery components. The “Regulator of Symbiosome Differentiation” transcription factor promotes expression of *VAMP721a*, as mentioned above (Section 5) during establishment of symbiosis [53]. The lack of two members of the R1R2R3-Myb transcription factor family, MYB3R1 and MYB3R4, suppresses the transcript level of the cytokinesis-specific t-SNARE *KNOLLE* [59]. The loss of function *myb3r1/myb3r4* impairs cell plate formation and therefore cytokinesis [59]. A transcription factor may regulate a key gene or several genes along a particular pathway, activating or repressing it. Several intriguing questions arise: (1) Is plant protein trafficking transcriptionally regulated? Several examples of gene regulation of the trafficking mechanisms at the transcriptional level support an affirmative answer (discussed in Section 5); (2) Which transcription factors are involved in coordinately regulating of protein trafficking? (3) When does this regulation take place? In humans the transcription factor TFEB is responsible for coordination of gene expression of a set of genes that code for trafficking mechanism proteins and regulators of lysosomal biogenesis and exocytosis [43]. The TFEB function is fundamental for cell functioning, with very severe developmental defects when it is defective [60]. Thus it is highly probable that transcriptional regulation also occurs in plants. The substantial transcriptional regulation of genes participating in plant endomembrane system corresponds to the eukaryotic conserved Unfolded Protein Response or Endoplasmic Reticulum Stress Response [61]. This process related to protein synthesis and folding, does not necessarily affect protein trafficking although a reduction of proteins entering the pathway can be drastically reduced due to Endoplasmic-Reticulum-Associated protein Degradation and the Unfolded Protein Response.

Overall, the existence of transcriptional regulation is likely the case. According to cell requirements, transcription factors can regulate the expression of members of trafficking mechanisms that coordinately modulate certain pathways, thus protein location or relocation. These transcription factors would allow endomembrane system plasticity in physiological processes. The challenge will be to identify the transcription factors involved in such a process. A suitable strategy to find protein trafficking transcriptional regulators could be a genetic screen covering all the transcription factors. Arabidopsis has 1400 transcription factors, which is similar to organisms with larger genomes such as rice, which has over two thousand transcription factors (AGRIS database http://arabidopsis.med.ohio-state.edu/AtTFDB/; Database of Rice Transcription Factors http://drtf.cbi.pku.edu.cn/). Since transcription factors usually function as heterodimers, multiple mutant combinations of them would be needed. This approach is even more complicated if there is gene redundancy. The screening has to be based on analyzing the subcellular phenotype under conditions where protein trafficking is modulated, which is laborious and time-consuming. The powerful tools developed by system biologists may facilitate tackling the challenge of finding trafficking transcriptional regulators. Even though it could be a biased approach, it will likely bring up candidates, especially thanks to all the available genome and transcriptome information. The function of all the identified transcription factors involved in protein trafficking as well as their impact on plant physiology needs to be analyzed further using genetic and cell biology strategies. Carrying out this research successfully may broaden the vision of protein trafficking modulation in plant cell biology.

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