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Review

AUXOLOGY: When auxin meets plant evo-devo

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ABSTRACT

Auxin is implicated throughout plant growth and development. Although the effects of this plant hormone have been recognized for more than a century, it is only in the past two decades that light has been shed on the molecular mechanisms that regulate auxin homeostasis, signaling, transport, crosstalk with other hormonal pathways as well as its roles in plant development. These discoveries established a molecular framework to study the role of auxin in land plant evolution. Here, we review recent advances in auxin biology and their implications in both micro- and macro-evolution of plant morphology. By analogy to the term 'hoxology', which refers to the critical role of *HOX* genes in metazoan evolution, we propose to introduce the term 'auxology' to take into account the crucial role of auxin in plant evo-devo.

Introduction

Body plan (or *Bauplan* in German) is essentially the blueprint for the way the body of an organism is laid out. It recapitulates the basic features for a phylum without precisely describing any one particular species of that division. Unlike animals, plants have an alternation of generations where the sporophyte ($2n$) and the gametophyte (n) are independent organisms that are characterized by a unique body plan. The patterning of the body plan mainly includes the establishment of axial properties (such as the apical–basal, the radial, and the proximal–distal axes) and the determination of cell fate by positional information.

In seed plants, the principal body axes of plants are patterned both early in embryonic development and during all the life cycle. Embryogenesis generates the apical–basal axis, the radial axis, the cotyledons (embryonic leaves) and the primary shoot and root meristems. During postembryonic development, these meristems produce lateral organs along the growing primary body axis and establish the proximal–distal axis. In contrast to animals, plants are thus able to develop reiterative morphological units throughout the entire lifespan. These modular units can also vary in form in response to variable environmental cues. Phenotypic plasticity in plant development might therefore constrain evolution in a very different way from animals insofar as the final shape of the whole plant is not so canalized.

In angiosperms, all these major patterning events involve the phytohormone auxin. Moreover, auxin mediates plant growth in response to environmental signals. Thus, the evolution of auxin homeostasis and response systems is thought to play a key role in the evolution of land plant architecture (Cooke et al., 2004, 2002).

Coincident with the increased understanding of the auxin signaling in model organisms has been the development of tools and data in non-seed plants. The recently sequenced genomes of the moss *Physcomitrella patens* (Rensing et al., 2008) and the lycophyte *Selaginella moellendorffii* (Banks et al., 2011) make comparative genomic approaches possible. In parallel, several tools for studying gene function have been developed in *P. patens*, such as RNAi, inducible promoters and gene targeting by homologous recombination.

It is therefore timely to review our understanding in the evolutionary genetics of development across the land plants. Here we attempt to survey a limited number of recent findings that investigate the extent to which changes in auxin signaling could have played a role in the radiation and diversification of the body plan in land plants. Due to the lack of functional data in most non-model species, this review mainly focuses on genes rather than on development, except when data about their role in development are available (e.g., *Arabidopsis* or *Physcomitrella*).

From auxin biosynthesis to signaling in the angiosperm *Arabidopsis thaliana*

Auxin pathway is controlled at many levels that include auxin biosynthesis, auxin metabolism, and auxin transport. Moreover,

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auxin was proposed to act as an integrator of the activities of multiple plant hormones, altogether suggesting a vast regulatory network of auxin during plant development (Jaillais and Chory, 2010).

Auxin biosynthesis

Indole-3-acetic acid (IAA) is the most potent naturally occurring member of the auxin family. High IAA levels are detected in shoot and root meristematic tissues, in cotyledons, as well as in young leaves that have the highest biosynthetic capacity (Ljung et al., 2001). In mature leaves and roots, IAA remains present but in smaller amounts.

The identification of molecular components of IAA biosynthesis revealed the existence of at least two separate major pathways. One is dependent on the precursor tryptophan (Trp) and the other is Trp-independent (see the review by Woodward and Bartel, 2005). Indeed, labeling experiments suggest that seedlings do not synthesize IAA solely from Trp (Normanly et al., 1993). Moreover, *trp2-1* and *trp3-1* mutants in Trp biosynthesis contain comparable levels of free IAA to that of wild-type plants, suggesting that a Trp-independent pathway occurs in plants. Analyses of the *trp2-1* mutant imply that IAA could be produced from indole-3-glycerol phosphate or indole (Ouyang et al., 2000).

In *Arabidopsis*, it is possible to distinguish two Trp-dependent pathways: the indole-3-acetaldoxime (IAOx) pathway and the indole-3-pyruvate (IPA) pathway. The IAOx pathway is carried out by the two P450 monooxygenases CYP79B2 and CYP79B3. Overexpression of CYP79B2 leads to an increase in free auxin levels and displays auxin overproduction phenotypes (longer hypocotyls, epinastic cotyledons), whereas *cyp79B*-deficient mutants have reduced levels of IAOx and IAA associated with shorter petioles and smaller leaves (Zhao et al., 2003). The intermediate IAOx can be converted to IAA either by the enzyme aldehyde oxidase protein AAO1 or indirectly by entering the indolic glucosinolates pathway in which the last step consists in hydrolyzing indole-3-acetonitrile (IAN) to IAA. The P450 monooxygenase CYP83B1, the C-S lyase SUR1 and the IAN nitrilases NIT1-3 have been shown to be involved in the latter pathway (Bak et al., 2001; Mikkelsen et al., 2004; Normanly et al., 1997). However, *CYP79B* genes are not conserved outside of Brassicales and IAOx intermediates are not found in rice, maize and tobacco, suggesting that the IAOx pathway is clade-specific and therefore might not be relevant at a macroevolutionary scale (Sugawara et al., 2009) (Table S1).

Recently, two independent genetic screens revealed the importance of IPA in auxin biosynthesis (Fig. 1A). Both screens identified mutants in a tryptophan aminotransferase called TAA1 that converts IPA into indole-3-acetaldehyde (Stepanova et al., 2008; Tao et al., 2008). Multiple mutants that disrupt three genes from the TAA1 family are severely impaired in both embryonic and post-embryonic development and they have phenotypes reminiscent of auxin signaling or transport mutants (Stepanova et al., 2008). The IPA pathway was recently shown to be very short, as IPA is directly converted into IAA by flavin monooxygenases from the YUCCA family (Fig. 1A) (Mashiguchi et al., 2011). Plants overexpressing YUCCA genes contain elevated levels of free auxin and display auxin overproduction phenotypes, a phenotype that is dependent on TAA1 activity (Stepanova et al., 2011; Won et al., 2011; Zhao et al., 2001). *yuc1yuc4yuc10yuc11* quadruple mutants lack a hypocotyl, a root meristem and floral organs, a phenotype very similar to some signaling or transport mutants (Cheng et al., 2007a). YUCCAs are rate-limiting enzymes in auxin biosynthesis and their expression is highly regulated by both environmental and developmental pathways. For example, the PIF transcription factors, which are master regulators of light-mediated development, control elongation by directly regulating *YUCCA* genes transcription (Hornitschek et al., 2012; Li et al., 2012; Sun et al., 2012). Besides, the transcriptional activator STYLISH1 promotes leaf and flower development by directly binding to the *YUCCA4* promoter (Eklund et al., 2010a).

Auxin transport

In plants, two distinct pathways are known to play a role in auxin transport: a passive distribution through vascular tissue and an active cell-to-cell polar transport. This polar auxin transport is fundamental for auxin distribution over both short and long distances. This transport occurs in a cell-to-cell manner and depends on specific influx and efflux carrier proteins that facilitate the uptake and release of auxin from/to the apoplast (Fig. 1B). Many auxin carriers are well characterized: the PIN-FORMED (PIN) proteins (Galweiler et al., 1998) and several proteins of the ABCB and ABCG transporter family (Cho et al., 2007; Geisler et al., 2005;

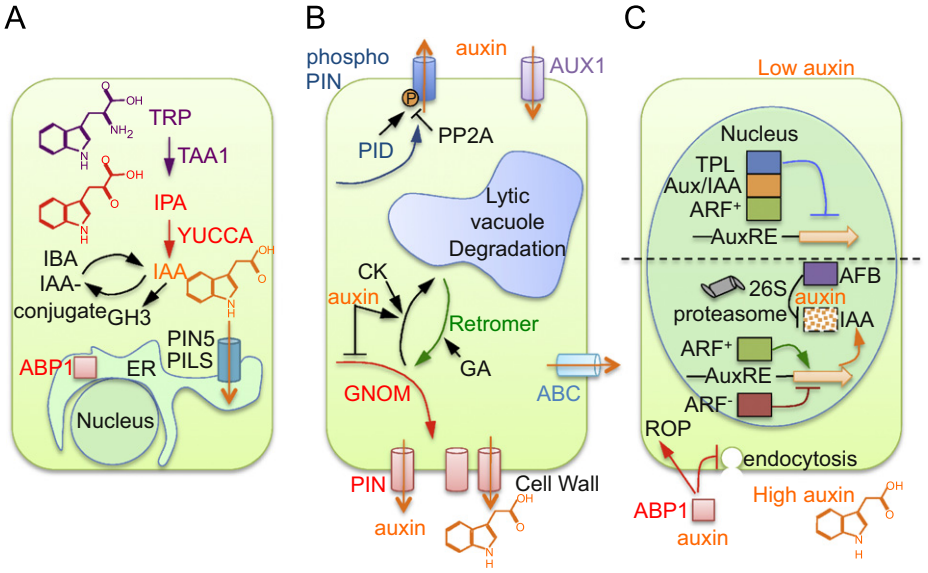

Fig. 1. Schematic representation of auxin signaling: (A) biosynthesis and homeostasis, (B) polar auxin transport and (C) perception. GA, gibberellin; CK, cytokinin; auxRE, Auxin Response Element.

Ruzicka et al., 2010) are involved in auxin efflux from the cell and the AUX1/LIKE AUXIN PERMEASE (AUX1/LAX) proteins are involved in auxin influx (Bennett et al., 1996; Swarup et al., 2001).

Among these carriers, PIN proteins have been proposed to be central rate-limiting components in polar auxin transport (Petrasek et al., 2006; Wisniewska et al., 2006). A key characteristic of these proteins is their polar localization in the cell (Fig. 1B). This polar localization correlates with putative auxin fluxes in the plants and are key to establish local auxin concentrations (Wisniewska et al., 2006). The processes behind the establishment and maintenance of PIN polarity at the cell level are extremely complex and rely on connections with the cell wall, the actin cytoskeleton, phosphoinositide and calcium signaling, slow diffusion in the plasma membrane as well as intracellular trafficking (Fig. 1B) (Dhonukshe et al., 2008a; Kleine-Vehn et al., 2011; Mravec et al., 2011; Zhang et al., 2011). A determinant factor for PIN polarity is their endocytic trafficking. The current model proposes that PIN proteins are secreted in a non-polar manner and that their subsequent endocytosis and recyling establish their polar localization at the rootward pole of the cell (Dhonukshe et al., 2008b). This polar recyling is dependent on the endosomal protein GNOM (Geldner et al., 2003; Kleine-Vehn et al., 2009). Phosphorylation of PINs by several kinases, including PINOID (PID), targets these auxin carriers to a GNOM-independent recycling pathway that target them to the shootward pole of the cell (Fig. 1B) (Kleine-Vehn et al., 2009). This action is antagonistically controlled by the regulatory subunit of protein phosphatase 2A (PP2A) (Fig. 1B) (Michniewicz et al., 2007).

Endocytosis and recycling also control the quantity of PIN protein at the plasma membrane by regulating the balance of protein that is recycled back to the plasma membrane or targeted to the lytic vacuole for degradation (Fig. 1B) (Abas et al., 2006; Jaillais et al., 2006, 2007). The retromer, a conserved protein complex, is involved in this balance as it promotes the retrieval of PIN proteins from late endosomes and reroute them toward the plasma membrane (Fig. 1B) (Jaillais et al., 2007). Auxin itself plays a key role in this regulation as it can inhibit endocytosis at certain concentration or promotes PIN proteins degradation at others (Abas et al., 2006; Paciorek et al., 2005; Robert et al., 2010). Moreover, MAB4/ENP/NPY1 and its closest paralogs were recently shown to control polar auxin transport and PIN protein localization as well as their quantity at the plasma membrane (Cheng et al., 2007b; Furutani et al., 2007, 2011; Li et al., 2011). Similarly to the PINs, MAB4/ENP/NPY1 family proteins are polarly localized. However it is still unknown how they regulate PIN intracellular trafficking. They belong to a plant specific family of 33 members that includes NPH3, a protein partner of the phot1 blue light photoreceptor involved in phototropism (Christie, 2007; Pedmale and Liscum, 2007). NPH3 was recently shown to function as a substrate-specific adapter in a CULLIN3-based E3 ubiquitin ligase (Roberts et al., 2011). As such, NPH3 can promote mono- and poly-ubiquitination of phot1, which modify both its subcellular localization and quantity at the plasma membrane (Roberts et al., 2011). It has been recently shown that monou-biquitination controls membrane protein trafficking in *Arabidopsis* (Barberon et al., 2011) and that PIN2 is ubiquitinated *in planta* (Abas et al., 2006; Leitner et al., 2012). Taken together, it is tempting to speculate that MAB4/ENP/NPY1 might modulate PIN protein localization by a ubiquitination-dependent regulation of their intracellular trafficking.

Other mechanisms controlling auxin levels and homeostasis

As discussed above, maintenance of correct cellular auxin levels requires biosynthesis and transport. Another important regulation level is auxin storage as inactive conjugates and indole-3-butyric acid (IBA), which can provide free IAA upon hydrolysis and β-oxidation, respectively (Fig. 1A). Hence, IAA can be ester-linked to sugars or amide-linked to amino acids leading to a great diversity in IAA conjugates (reviewed in Woodward and Bartel, 2005). Remarkably, the conjugation to amino acids involves enzymes of the GH3 family, whose members have been identified as early auxin responsive genes (Abel and Theologis, 1996), suggesting that auxin levels are maintained in part by a negative feedback loop (Fig. 1A). Overexpression of GH3.2 (YDK) or GH3.6 (DFL1) results in phenotypes consistent with decreased free auxin levels, such as reduced lateral roots and hypocotyl elongation (Nakazawa et al., 2001; Takase et al., 2004). Contrary to GH3 enzymes, IRL1/ILL amidohydrolases carry out the release of free IAA from conjugates (reviewed in Ludwig-Muller, 2011). Noticeably, there is evidence that some of the auxin conjugates such as IAA-aspartate and IAA-glutamate are intermediates in IAA degradation rather than storage conjugates (reviewed in Ludwig-Muller, 2011).

It was recently shown that PIN5, contrary to other PINs, is not localized at the plasma membrane but is localized at the surface of the endoplasmic reticulum (ER) (Fig. 1A) (Mravec et al., 2009). PIN5 might mediate auxin flow from the cytosol into the lumen of the reticulum and therefore might modulate intracellular auxin homeostasis by limiting the auxin availability for cell-to-cell transport or nuclear signaling. PIN8 is also an atypical PIN that is localized in the ER and controls auxin homeostasis in pollen (Bosco et al., 2012; Ganguly et al., 2010; Mravec et al., 2009). Besides, a family of PIN-LIKES proteins (PILS) also localized in the ER was recently described as regulators of intracellular auxin homeostasis (Barbez et al., 2012). Taken together, these results show that the conjugation/hydrolysis and storage of IAA is therefore a central way to regulate auxin concentration at the cellular level.

Auxin perception and signaling

The transcriptional auxin signaling pathway is mainly mediated by the auxin co-receptors of the TIR1-AFB family (Dharmasiri et al., 2005; Kepinski and Leyser, 2005), the auxin signaling repressors of the Aux/IAA family, the transcription factors of the AUXIN RESPONSE FACTOR (ARF) family, and the transcription co-repressor TOPLESS (TPL) (Fig. 1C) (Szemenyei et al., 2008). In absence of auxin, Aux/IAA form a trimeric complex, presumably onto DNA, with DNA-binding ARF proteins and the transcriptional co-repressor TPL (Szemenyei et al., 2008), thus repressing the transcription of auxin-induced genes (Fig. 1C, top) (Ulmasov et al., 1997). Auxin interacts both with TIR1/AFBs and Aux/IAA proteins acting as molecular glue between the two proteins (Dharmasiri et al., 2005; Kepinski and Leyser, 2005; Tan et al., 2007). Auxin therefore promotes Aux/IAAs ubiquitination by TIR1/AFBs E3-ubiquitin ligases and subsequent degradation by the proteasome (Dharmasiri et al., 2005; Kepinski and Leyser, 2005). Different combinations of TIR1/AFB and Aux/IAA proteins form co-receptor complexes with a wide range of auxin-binding affinities that are mainly determined by Aux/IAA proteins (Calderon Villalobos et al., 2012). In the absence of Aux/IAA and TPL, ARFs can act as transcriptional regulators (Fig. 1C, bottom) (Gray et al., 2001). ARFs can be transcriptional activator (ARF^+) or repressors (ARF^-). It was recently shown that the majority of activators ARFs interacts with most Aux/IAAs, while most repressor ARFs do not or in a limited way (Vernoux et al., 2011). This work suggests that repressor ARF activity might be regulated independently of auxin and that they act by competing with activator ARFs for binding to TGTCTC auxin responsive elements (AuxREs) at promoters of auxin responsive genes (Fig. 1C). Therefore, the respective concentration of ARF^+ and ARF^- might influence the threshold of auxin sensitivity in a given cell or tissue.

The widely used synthetic auxin-responsive promoter *DR5* might therefore be seen as a reporter of the ratio between acting ARF^{+} and ARF^{-} in a cell rather than a reporter for auxin as it is often referred to. A newly described auxin sensor (DII-VENUS) consists of a fusion between the Aux/IAA auxin interaction domain and the fast maturating fluorescent protein mVENUS (Brunoud et al., 2012). DII-VENUS is degraded when auxin is perceived and is therefore a response input sensor, while the *DR5* promoter monitors the output response. Direct comparison between DII-VENUS and DR5 activity exemplifies that auxin perception is not necessarily translated into gene induction, which might in part be due to the repressive activity of ARF^{-} in those cells (Brunoud et al., 2012; Vernoux et al., 2011), as well as the auxin sensitivity based on the expressed TIR/AFB-Aux/IAA co-receptor system (Calderon Villalobos et al., 2012).

Another auxin receptor is the AUXIN-BINDING PROTEIN1 (ABP1) that binds auxin with high affinity and specificity (Hertel et al., 1972). Plants overexpressing ABP1 exhibit an auxin-dependent expansion in the size of differentiated cells that are normally unresponsive (Jones et al., 1998), whereas loss of ABP1 function causes embryonic arrest and results in defects in cell division and cell elongation (Chen et al., 2001). Moreover, inducible inactivation of ABP1 affects plant growth by interfering with the cell cycle during postembryonic shoot (Braun et al., 2008; David et al., 2007) and root (Tromas et al., 2009) development. ABP1 is secreted in the lumen of the reticulum and found in the apoplast (Fig. 1A and C). It is not clear how auxin binding to ABP1 is transduced, but it was recently shown that ABP1 signaling could act independently of the TIR1/AFB system at a post-transcriptional level (Robert et al., 2010; Xu et al., 2010). Indeed, auxin binding to ABP1 inhibits endocytosis, which among other effects (Fig. 1C), regulates the amount of PINs at the surface of the cell and therefore promotes its own efflux (Paciorek et al., 2005; Robert et al., 2010). Moreover, ABP1 acts upstream of the small GTPase of the RHO-OF-PLANT (ROP) class in regulating cell morphogenesis (Xu et al., 2010). However, loss of *ABP1* function also impairs the up-regulation of early auxin responsive genes (Effendi et al., 2011; Tromas et al., 2009). So far, it is unknown how ABP1 is regulating gene expression and further experiments are required to determine whether there is a signaling pathway from ABP1 to the nucleus, perhaps implying ROP GTPases (Xu et al., 2010) or whether this effect on auxin inducible genes is the result of feedback between ABP1 and TIR1/AFBs signaling (Effendi et al., 2011).

A third pathway acting independently from TIR1 is mediated by the putative dual-specificity protein phosphatase INDOLE-3-BUTYRIC ACID RESPONSE5 (IBR5). Mutations in *IBR5* confer resistance to auxin and result in decreased plant height, defective vascular development, and fewer lateral roots (Monroe-Augustus et al., 2003). Contrary to the TIR1 signaling, Aux/IAA repressor proteins are not destabilized after response to auxin through this pathway (Strader et al., 2008). The targets involved downstream of IBR5 are not yet identified.

Auxin: a key role in the development of flowering plants

The polar auxin transport generates local auxin concentrations that are instrumental in morphogenesis. Formation of an auxin gradient has been proposed to be necessary for cell specification within the root meristem (Blilou et al., 2005; Friml et al., 2002; Grieneisen et al., 2007; Sabatini et al., 1999) and the secondary xylem (Uggla et al., 1996), and to regulate planar polarity in the root (Ikeda et al., 2009) as well as patterning of the embryo sac (Pagnussat et al., 2009). Initially, these studies suggest that auxin acts as a morphogen, conferring patterning information in a concentration-dependent manner. However in many cases, the emerging view is that auxin acts more like a threshold-specific trigger (Lau et al., 2011). According to the morphogen hypothesis, a given cell converts auxin gradients into different cellular outputs given its position within the established gradient. However in the threshold-specific trigger hypothesis, auxin does not necessarily have to establish a gradient but to go above or under a certain threshold concentration to induce the morphogenetic event. Therefore, the trigger concept is a morphogen concept with a discrete or one-step response. Thus, it is often the establishment of auxin maximum (Benkova et al., 2009) or minimum (Sorefan et al., 2009) that is important for organogenesis. Importantly, the auxin threshold can be set at different levels (Vernoux et al., 2011) and trigger various cellular and developmental outputs depending on the local signaling capacity of a given cell (Brunoud et al., 2012), such as the presence of different Aux/IAA-ARF pairs (Rademacher et al., 2012), of different Aux/IAA-TIR1/AFB co-receptors (Calderon Villalobos et al., 2012) or the signaling state of other hormones (Nemhauser et al., 2004).

Polar auxin transport: from the cell to the tissue level

The establishment of auxin minima and maxima involves the coordination of auxin fluxes at the tissue level. Several experiments and computer-based models have been proposed to explain the link between PIN protein distribution, local auxin accumulation and cellular output. The canalization model proposes that auxin transporters act by amplifying and stabilizing existing auxin fluxes, *i.e.*, a positive feedback between flux and transport (Sachs, 1969). The canalization model is both supported by experimental data for the formation of venation pattern (Sauer et al., 2006; Scarpella et al., 2006) as well as by simulation data for the auxin fluxes in the apical meristem (Stoma et al., 2008). More recently, the extracellular receptor-based polarization (ERP) model (Wabnik et al., 2010) proposes a mechanistic view of the canalization model by taking into account auxin feedback on PIN transcription (Peer et al., 2004) and auxin feedback on PIN endocytosis (Paciorek et al., 2005) through extracellular auxin perception.

Alternatively to the canalization (or flux-based) model, the "up-the-gradient" (or concentration-based) model proposes that cells are able to sense auxin concentrations in surrounding cells and subsequently drive auxin against the gradient by directing plasma membrane PIN proteins to the membrane adjacent to the neighboring cell with highest auxin concentration (Jonsson et al., 2006; Smith et al., 2006). One remaining question is to understand how cells could sense auxin concentrations in their surrounding environment. A recent study reveals that biomechanics mediates the coupling between PIN1 localization and cortical microtubule orientation (Heisler et al., 2010). By inducing cell growth and subsequent arrangement of microtubules, auxin triggers the accumulation of PIN proteins at the plasma membrane adjacent to the expanding neighbor. Thus, the sensor-cell exports auxin toward the expanding neighbor, both increasing its auxin concentration and mediating the feedback loop between auxin and its transport.

Auxin and embryogenesis

Apical–basal axis formation is tightly linked to dynamic changes in auxin concentration and flux (Fig. 2A) (reviewed in Bowman and Floyd, 2008). First, an asymmetric distribution of the efflux carrier PIN7 mediates auxin flow into the apical cell until first zygotic divisions (Friml et al., 2003). Second, auxin is drained from the embryo due to asymmetric distribution of PIN1 during the globular stage (Friml et al., 2003). Third, auxin flow is directed towards the top of the embryo through the protodermal layer, and then downwards through the center (Benkova et al., 2003; Friml et al., 2003). Last, reversal in PIN1 polarity at the apex of the globular embryo defines a zone depleted in auxin: the future shoot

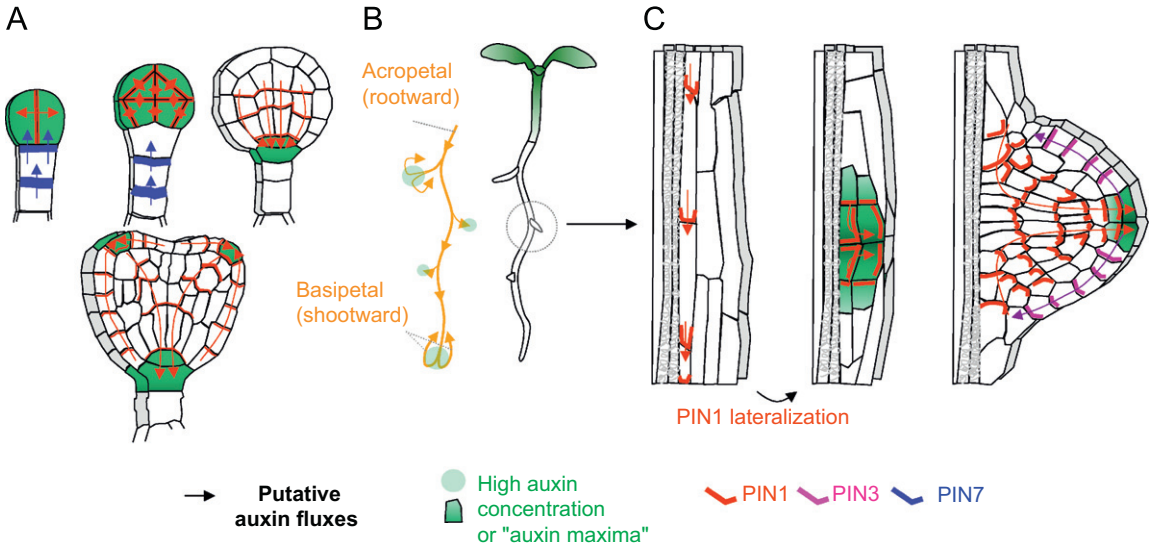

Fig. 2. Pleiotropic role for auxin in plant development. Putative auxin fluxes as deduced from functional studies and localization of PIN proteins in the developing embryo (A), root system (B) and lateral root (C). PIN1 protein is in red, PIN3 protein is in purple, PIN7 protein in blue and the putative auxin fluxes associated with these carriers are represented by red, purple and blue arrows respectively. Auxin maxima are in green.

apical meristem. Although the asymmetric distribution of IAA cannot occur without polar transport, the relative importance of local auxin production during embryogenesis has been revealed only recently. Multiple *yuc* mutants have severe embryo and cotyledons defects (Cheng et al., 2007a; Stepanova et al., 2008, 2011) and the protein LEAFY COTYLEDON2, a key transcription factor in embryo development, has been shown to induce auxin responses by binding directly to the *YUC4* promoter (Stone et al., 2008). In conclusion, both convergent auxin flow and localized auxin synthesis lead to the creation of auxin maxima that correspond to future root meristem, cotyledons and vasculature.

Local auxin accumulation activates the two transcription factors MONOPTEROS (MP)/ARF5 and NONPHOTOTROPIC HYPOCOTYL4 (NPH4)/ARF7 by degrading the Aux/IAA transcriptional repressor BODENLOS (Hamann et al., 2002). MP and NPH4 maintain *PLETHORA* (*PLT*) gene expression in the basal region of the developing globular embryo. PLT transcription factors are essential for quiescent center specification and definition of the stem cell niche in the root meristem (Aida et al., 2004). On the one hand, the expansion of *PLTs* gene expression into the progenitor cell of the quiescent center is induced by auxin and relies on ARF action (Aida et al., 2004). In turn *PLT* genes trigger the expression of *PIN* genes that establish the auxin maximum in the root meristem, thereby restricting the expression of the *PLT* genes (Blilou et al., 2005). On the other hand, PLT proteins are expressed in a gradient pattern, which overlaps the auxin gradient, with highest expression in the stem cell area, intermediate levels in the division zone, and low levels in the elongation zone (Galinha et al., 2007). Taken together, these results suggest that developmental gradients are the result of feedback interactions in auxin signaling (Benjamins and Scheres, 2008).

Local auxin concentrations play also a role in establishing the expression patterns of key transcription factors in the apical region of the embryo. For instance, the transcription factors CUC are essential in creating boundaries into the developing embryo of *A. thaliana* and their expression is correlated with low auxin levels (Furutani et al., 2004). The same correlation is observed for class I KNOX genes (such as SHOOT MERISTEMLESS) that promote the formation of the future shoot apical meristem in a region of low auxin concentration and low PIN-mediated transport (Hay et al., 2006). In contrast, class III homeodomain-leucine zipper genes have expression patterns that correlate with known pathways of auxin flow out of the apex toward incipient leaf primordial and in the provasculature (Heisler et al., 2005).

In conclusion, interplay between sites of auxin maxima and specific patterns of both auxin-responsive genes and other patterning genes subdivide the embryo along both the apical–basal and radial axes.

Auxin and postembryonic development

Shoot and root growth and development are a reiteration of basic patterning processes established during embryogenesis (Benkova et al., 2003). Thus, auxin continues to play a key role in generating postembryonic lateral organs.

The primary root usually branches to form lateral roots that extend horizontally from the latter one (Fig. 2B and C). Lateral roots play a role in facilitating anchoring and absorptive properties of the plant. Lateral roots originate exclusively from pericycle founder cells (Dolan et al., 1993) and their initiation begins when either individual or pairs of pericycle founder cells undergo several rounds of anticlinal divisions (Malamy and Benfey, 1997). Every pericycle cell has the ability to divide in response to elevated auxin levels (Boerjan et al., 1995). However, only few of these cells become founder cells. Auxin has been shown to regulate spacing of pericycle founder cells by generating auxin accumulation sites in the protoxylem that prime the adjacent pericycle cells to become founder cells (De Smet et al., 2007). Local auxin accumulation causes the degradation of IAA14, thereby releasing the repression on ARF7 and ARF19, and allowing them to directly activate the expression of LBD/ASL18 and LBD/ASL16 transcription factors (Okushima et al., 2007). Auxin plays therefore a crucial role in regulating lateral root patterning (recently reviewed in Péret et al., 2009). Auxin also acts as a local inductive signal that reprograms cells overlaying lateral root primordia to facilitate organ emergence (Swarup et al., 2008). Last, auxin could be necessary for the activation of the lateral root meristem and the elongation of the new primordium (Péret et al., 2009).

As a last example, we would mention the key role of auxin in the patterning of the angiosperm female gametophyte. It has been recently shown that auxin is implicated in polarizing the female gametophyte by creating a gradient-based distribution (Pagnussat et al., 2009). Thus, auxin concentration determines cell fates, with

the highest auxin levels specifying synergids, followed by egg cells, and the lowest auxin resulting in antipodal cells. Remarkably, this gradient does not seem to be established by polar auxin transport but mainly by spatially differential activities of *YUCCA* genes (Pagnussat et al., 2009).

Auxin and crosstalk with other hormone pathways

Auxin interacts at many levels with all the other plant hormone pathways and therefore broadly impacts morphogenesis (Jaillais and Chory, 2010). Most hormone pathways heavily affect auxin homeostasis mainly by modifying expression of auxin transport, biosynthesis or signaling components (Vert and Chory, 2011). For example, cytokinins induce the expression of IAA3, a negative regulator of the auxin-signaling pathway at the transition zone of the root, thereby providing a frontier for auxin-induced cell proliferation *versus* differentiation (Dello Ioio et al., 2008; Moubayidin et al., 2010). Ethylene, too, controls auxin levels by manipulating the expression of both auxin transporters (from the AUX and PIN families) and biosynthetic enzymes (for example, the auxin biosynthesis enzyme TAA1) (Ruzicka et al., 2007; Stepanova et al., 2008, 2007; Swarup et al., 2007). Additionally, auxin feeds back on ethylene biosynthesis in a complicated mechanism that controls the auxin-ethylene level in root cells.

A new emerging paradigm is the regulation of PIN proteins trafficking by other plant hormones. Indeed, cytokinins were recently shown to control PIN protein endocytosis and to induce their degradation in lytic vacuoles (Fig. 1B) (Marhavy et al., 2011). High concentrations of jasmonate also induce PIN2 endocytosis and degradation (Sun et al., 2011). On the contrary, gibberellin signaling and the secretory peptides from the GOLVEN family limit PIN trafficking to lytic vacuoles (Fig. 1B) (Whitford et al., 2012; Willige et al., 2011). Therefore, not only auxin itself regulates its own efflux, but also many other hormones control the intracellular trafficking of PIN and therefore local auxin accumulation required to trigger morphogenetic events. Interestingly, some of these regulations do not require transcription (Marhavy et al., 2011; Robert et al., 2010). Therefore, there are at least two complex regulatory networks involved in hormone crosstalk in the case of auxin, one transcriptional and one on the regulation of PINs intracellular trafficking, particularly on the balance between recycling and degradation.

Given that auxin is involved in numerous aspects of plant growth and development, it is not surprising that auxin regulation turns out to be so complex and so intertwined with that of other plant hormones. How these different levels of regulation elaborated during the course of land plant evolution is consequently a fascinating question and will be discussed in the following section.

Evolution of the auxin pathway in land plants

Land plants (embryophytes) are thought to have evolved from ancestral charophycean green algae (Finet et al., 2010b; Graham, 1993). Subsequently to the colonization of land, embryophytes underwent radiation and rapid diversification of body plans. The main features of body plans and phylogenetic relationships among extant phyla of land plants are illustrated in Fig. 3. Auxin was detected in virtually all branches of the green lineage and it has been clear for decades that all land plants respond in dramatic ways to auxin application (Cooke et al., 2002). Moreover, auxin

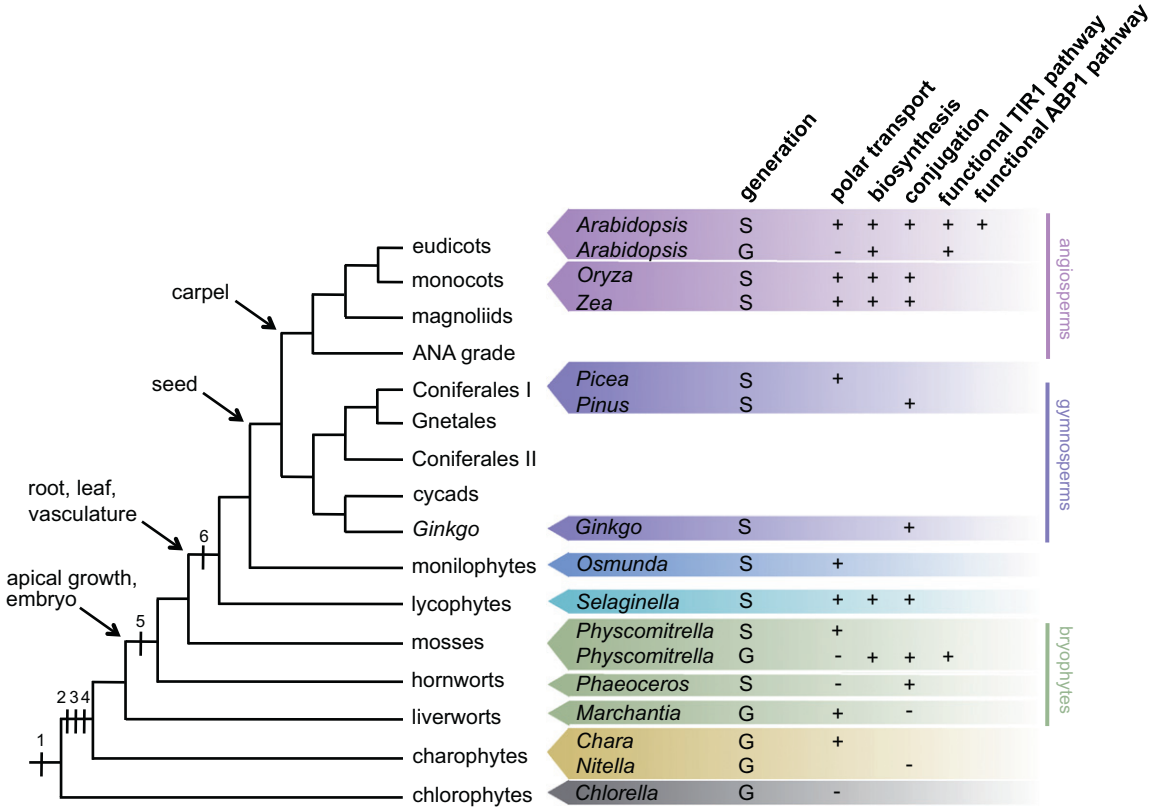

Fig. 3. Evolutionary changes in auxin biology in green plants. *Key to characters*: 1, acquisition of the BTB-NPH3-like gene family; 2, acquisition of the TPL/TPR gene family; 3, acquisition of the PIN proteins involved in auxin efflux and homeostasis; 4, acquisition of the ability for cells to store IAA by conjugation; 5, acquisition of the ER-localized IRL1-like IAA amidohydrolases; 6, predominance of IAA-aspartate/glucose/glutamate over amide conjugates, some key enzymes involved in the release of free IAA after IAA-amino acid conjugates hydrolysis. On the left, the presence (+) or absence (−) of a given character is only mentioned when it has been experimentally tested, S: sporophyte, G: gametophyte.

ability to act as a morphogen could date back to the origin of seed plants, as suggests the establishment of an auxin concentration gradient for the specification of secondary xylem during wood formation in Scots pine (Uggla et al., 1996). However, the molecular mechanisms underlying the biology of auxin in early-diverged lineages of land plants remain elusive, as well as where in the ancestral charophycean lineage the components of auxin biosynthesis/transport/response were assembled.

Origin of auxin metabolism

With regard to the Trp-dependent pathway, the YUCCA gene family is ancient in land plants, with homologs identified in the moss *Physcomitrella* (Rensing et al., 2008) and the lycophyte *Selaginella* (Banks et al., 2011). In order to tackle the overall pathway, we conducted bioinformatic analyses of the available genomic data in the plant kingdom. Most of the genes involved in IPA-dependent pathway in flowering plants are found in land plants (Table S1). Although data are very sparse in marchantiophytes and anthocerotophytes, it seems likely that the Trp-dependent pathway is very much the same in all land plants. Nevertheless, the molecular function of these different genes remains to be established in non-model species. Only the functional characterization of *PpSHI1* and *PpSHI2* has been reported in *P. patens*. The two PpSHI genes cooperatively induce IAA biosynthesis in the gametophyte (Eklund et al., 2010b). Although there are hardly any of these orthologs in algae, genes encoding the putative amidohydrolase AMI1, Trp-synthase α TSA1, and Trp-synthase β TSB1 have been identified in chlorophytes (Table S1). Since these enzymes are involved in the indole-3-acetamide (IAM) pathway, auxin might be synthesized via the IAM pathway in algae as it occurs in microorganisms (Patten and Glick, 1996). Finally, the Trp-independent pathway is poorly characterized in model plants, which limits evolutionary genomic approaches.

IAA conjugation seems to be a widespread process to control free IAA levels in land plants (see the review by Ludwig-Muller, 2011). However, noteworthy differences stand about the nature of major conjugates that consists either in amide conjugates (liverworts, mosses, hornworts) or IAA-aspartate/glucose/glutamate (lycophytes, ferns, seed plants). But the main striking feature is the slow conjugation rate in liverworts, suggesting that the strategy biosynthesis/degradation is predominantly used in this phylum (Sztein et al., 1999). Given that the biosynthesis/degradation of IAA is assumed to occur in charophyte algae, liverworts could have retained the putative ancestral strategy for controlling free IAA levels (Cooke et al., 2002). On the contrary, the other phyla in land plants evolved the potential to regulate free IAA levels by adjusting the equilibrium conjugation/hydrolysis. The results we obtained using *in silico* methods corroborate only partially the latter evolutionary schema. Indeed, group II GH3 proteins are absent from chlorophytes but present in all embryophyte lineages, including marchantiophytes (Table S1). Hence, it would be interesting to test whether class II GH3 enzymes are capable to catalyze conjugation in species belonging to marchantiophytes. Remarkably, like in flowering plants, GH3 proteins act as auxin conjugate synthetases in *P. patens* (Ludwig-Muller et al., 2009a, 2009b). Concerning hydrolysis, IRL1/ILL IAA amidohydrolases are present both in extant algae and land plants whereas conjugates hydrolysis does not seem to occur in algae (Sztein et al., 1995). IRL1/ILL IAA amidohydrolases could have been recruited later in the land plants for controlling IAA free levels.

Origin of the polar auxin transport

Polar transport of auxin can be directly measured by tracing radioactive synthetic IAA. Basipetal auxin transport was thus reported in the sporophytes of mosses (Fujita et al., 2008; Poli et al., 2003) and those of lycophytes (Wochok and Sussex, 1973). Besides, basipetal auxin transport was suggested to occur in moss rhizoids (Eklund et al., 2010b; Rose and Bopp, 1983). On the contrary, no polar auxin transport was detected in moss shoots in the gametophyte (Fujita et al., 2008). Both the influx and efflux carriers are sensitive to several inhibitors. The compounds 1-N-naphthylphthalamic acid (NPA) and 2,3,5-triiodobenzoic acid (TIBA) have traditionally been used to inhibit the efflux component of the polar auxin transport mechanism. Treatments with auxin transport inhibitors cause changes in the putative distribution of auxin in the sporophyte and result in abnormal embryo development (Fujita et al., 2008). On the contrary, no changes are noticed in the haploid shoot (Fujita et al., 2008). To conclude, the establishment of the apical–basal axis in moss sporophytes requires proper distribution of auxin during embryogenesis. This patterning is ensured by a mechanism of polar auxin transport, the molecular components of which are still poorly known in *P. patens*. Genomic approaches pinpoint the presence of three and five *PIN* homologs in the *Physcomitrella* (Rensing et al., 2008) and *Selaginella* (Banks et al., 2011; Floyd and Bowman, 2007) genomes, respectively. Although *Physcomitrella* PIN proteins share characteristics with PM-localized PINs (a central hydrophilic loop and a conserved domain around the putative tyrosine motive NPNTY), one of them is predominantly localized at the ER (Mravec et al., 2009). The ER localization of one moss PIN protein suggests that the function of PINs in mediating auxin homeostasis was present in the last common ancestor of land plants. Some authors recently proposed that ER-localized moss PIN proteins could also play a role in generating an intercellular auxin transport by ER-localized auxin transporters (Wabnik et al., 2011). This putative ancestral mechanism presumes that ER acts as an auxin reservoir and the release of auxin to the cytoplasm could facilitate non-polar auxin transport by generating channel-like auxin transport routes (Wabnik et al., 2011).

Interestingly, polar auxin transport has been recently detected in the charophyte *Chara corallina* (Boot et al., 2012) and partial PIN-like sequence was identified in the charophyte *Spirogyra pratensis* (De Smet et al., 2011). If corroborated by future studies, this finding suggests that PIN proteins predate the origin of land plants and could potentially play a role in polar auxin transport in charophytes. Additionally, four and two homologs of the auxin influx carriers *AUX1/LAX* have been detected in the *Physcomitrella* (Rensing et al., 2008) and *Selaginella* (Banks et al., 2011) genomes, respectively. As for ABCB and ABCG transporters, they predate the origin of land plants and have been identified in chlorophytes (De Smet et al., 2011).

Origin of auxin signaling

One surprising feature from the genome sequences of *P. patens* and *S. moellendorffii* is evidence for the presence of auxin signaling machinery identical to that in flowering plants (Banks et al., 2011; Rensing et al., 2008). In the present study, a comprehensive search of the marchantiophyte EST database also reveals the presence of genes encoding Aux/IAA proteins, ARF proteins, TIR1/AFB proteins, and components of the SCF^{TIR1} complex (Table S1). Thus, a complete TIR/AFB-ARF-Aux/IAA signaling cascade was probably already present in the last common ancestor of land plants. More importantly, molecular function of these components seems to be partially conserved in land plants. The use of auxin antagonists in angiosperms and *P. patens* suggests that auxin response mediated by TIR1, Aux/IAA and ARF proteins is an ancient mechanism (Hayashi et al., 2008). A recent study has shown that the moss Aux/IAA proteins interact with *Arabidopsis* TIR1 moss homologs called PpAFB and that a reduction in PpAFB levels and/or mutations

in Aux/IAA genes lead to an auxin-resistant phenotype (Prigge et al., 2010). Additionally, the expression of some ARF genes is regulated by small RNA-guided cleavage both in flowering plants and in *P. patens* (Axtell et al., 2007).

Finally, genomic analyses revealed the presence of genes encoding ABP1 and IBR5 proteins in bryophytes (Rensing et al., 2008) and lycophytes (Banks et al., 2011), suggesting that the three known auxin signaling pathways were present in the last common ancestor of extant land plants.

Auxin biology in algae

What evidence does exists for an auxin signaling network in algae? Auxin was demonstrated to induce cell division and interact with cytoskeleton in the charophyte lineage (Jin et al., 2008). Auxin also promotes cell division and prevents the formation of lateral branches in rhodophytes (Yokoya and Handro, 1996). In brown algae, which are members of an eukaryotic lineage distinct from Viridiplantae, IAA is required to ensure both proper branching pattern by relaying cell–cell positional information (Le Bail et al., 2010) and proper establishment of polarity of the developing embryo, as suggested by the use of exogenous application of auxin or auxin transport inhibitors (Basu et al., 2002; Sun et al., 2004). Genomic analyses reveal the absence of the TIR1-Aux/IAA-ARF mediated auxin signaling pathway in green algae (Lau et al., 2009; Rensing et al., 2008; Riano-Pachon et al., 2008). On the contrary, putative *ABP1* and *IBR5* orthologs have been identified in green algae (Lau et al., 2009; Monroe-Augustus et al., 2003) and could account for any auxin-mediated signaling. The ability to infer the ancestral developmental tool kit of extant chlorobionts and of extant land plants has been made possible by the complete genome sequencing of several green algae and early-diverged lineages of land plants, respectively (Bowman et al., 2007; Floyd and Bowman, 2007). Unfortunately, these data do not allow us to reveal the auxin machinery in charophytes, especially in the case of a gene absent in green algae and present in land plants. Class III homeodomain-leucine zipper, TPL/TPR, PIN, and NPH3-like gene families are thus far the only examples of auxin-related genes that appeared before the split between charophytes and streptophytes (charophytes and embryophytes) (Floyd et al., 2006).

Auxin was recruited independently during evolution

Examples from macro-evo-devo

In marked contrast to bryophytes that form a shoot in the haploid generation, vascular plants develop shoots in the diploid generation. Moreover, polar auxin transport is involved in the shoot development in flowering plants, whereas it is not the case in moss shoots in the gametophyte (Fujita et al., 2008). However, auxin is present in *P. patens* shoots and was detected in the basal part of the gametophore stem (Bierfreund et al., 2003; Fujita et al., 2008). These studies suggest that different developmental mechanisms have been recruited to produce shoots in bryophytes and vascular plants, even if auxin could play a role in both cases.

Another example is provided by the rooting system in plants. Tracheophytes (vascular plants) develop roots specialized in absorption of water and nutrients and anchoring of the plant to the ground. By contrast, bryophytes have rhizoids and not true roots since rhizoids are not produced by root meristems. In both cases, auxin is involved both in the development and growth of roots (Sabatini et al., 1999) and rhizoids (Sakakibara et al., 2003). Similarly to bryophytes, it has been reported that algae can have rhizoids whose development and growth is also affected by auxin (Basu et al., 2002; Klämbt et al., 1992). Given that roots and rhizoids are not homologous structures, it seems likely that auxin have been independently recruited.

Rather, rhizoids are thought to be homologous to root hair cells. Their development share common features (Fig. 4) such as the key role of ROOT HAIRLESS (RSL) transcription factors in specifying the future hair cells (*vs.* non-hair cells) (Jang et al., 2011; Menand et al.,

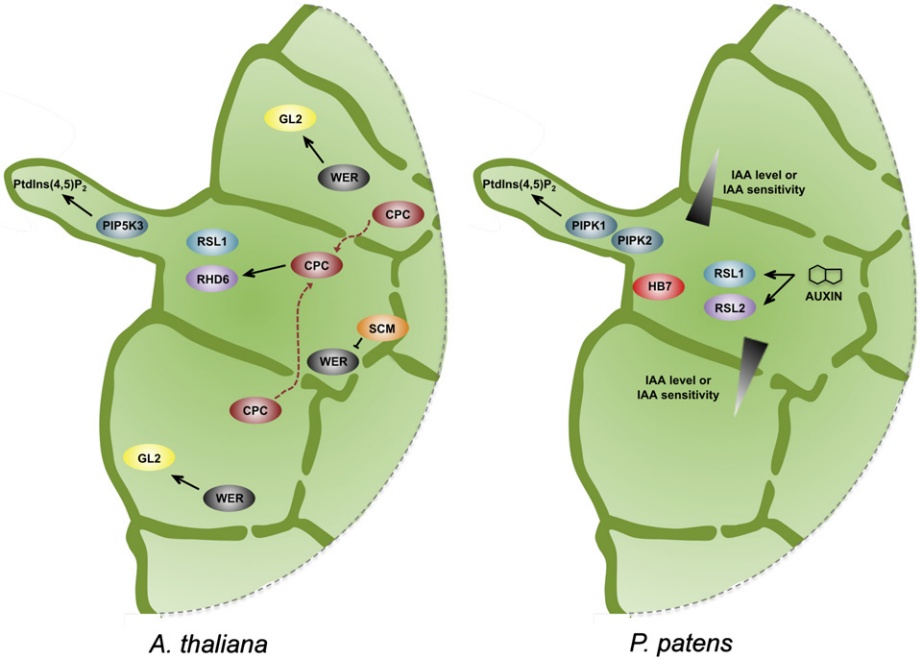

Fig. 4. Comparative development of *Arabidopsis* root hair cell and *Physcomitrella* rhizoid. Contrary to the WEREWOLF (WER) transcription factor that specifies non-hair fate in the root by inducing *GLABRA2* (*GL2*) gene expression, CAPRICE (CPC) acts as an activator of hair fate by inducing the expression of *ROOT HAIR DEFECTIVE 6* (*RHD6*). The SCRAMBLED (SCM) receptor is thought to respond to a cortical layer positional cue by repressing *WER* expression in the future hair cell. Hair cell elongation involves the lipid messenger PtdIns(4,5)P_2 synthesized by the PIPK5K3 enzyme. Similarly, *Physcomitrella* RHD SIX-LIKE1 (RSL1) and RSL2 transcription factors promote rhizoid differentiation, whilst PIPK1 and PIPK2 are essential for rhizoid elongation.

2007) and the one of phosphatidylinositol-4-phosphate 5-kinase (PIPK) enzymes in promoting elongation (Kusano et al., 2008; Saavedra et al., 2011; Stenzel et al., 2008). Similarly, auxin plays a role in the development of both hair cells and rhizoids but does not act at the same level in the developmental network. Although auxin positively regulates the expression of *RSL* genes early during rhizoid specification (Jang et al., 2011), auxin is not involved in hair cell specification in *Arabidopsis* (Jang et al., 2011) but modulates hair cell planar polarity (Ikeda et al., 2009). If rhizoids and root hair cells are homologous structures, these data suggest that either auxin might have played a role in the development of the first land plant soil anchoring system and that the regulatory network diverged later between mosses and flowering plants or auxin has been recruited independently in mosses and in angiosperms but the linkage occurred at different level in the regulatory network.

A last example of convergence could be the role of auxin during embryonic development. As presented above, proper patterning of the embryo in angiosperms is largely dependent upon auxin. By definition, embryophytes have evolved an embryo, which is a zygote producing further mitotic tissues, whereas algae have a zygote that enters immediately meiosis. However, some brown algae are known to develop an embryo, *e.g.,* in the *Fucus* and *Laminaria* genera. In *F. distichus*, it has been reported that the patterning of the embryo is impaired when exogenous IAA or transport inhibitors are applied (Basu et al., 2002; Sun et al., 2004). Such results raise an important question about plant evolution in a broader sense: is it possible that embryos of both embryophytes and brown algae represent elaborations of some zygotic developmental mechanism present in the last common ancestor of these groups? If so, the involvement of IAA in zygote patterning would be a plesiomorphic feature that might have been present in the common ancestor. Alternatively, the auxin pathway may have been independently recruited for embryo patterning both in brown algae and in embryophytes. The presence of IAA in brown algae, coupled with the lack of conservation of IAA transport and signaling pathways in *Ectocarpus siliculosus* (Le Bail et al., 2010), could support the independent recruitment of IAA in both brown algae and the green lineage.

Auxin as a main player in micro-evo-devo

In addition to its putative role in land plant radiation, auxin was shown to underpin morphological diversification within flowering plants. The best-known example is the differential distribution of auxin as a source of diversity of leaf morphology in closely related species. The current model for the development of *A. thaliana* leaf margin protrusions involves the accumulation of auxin by the efflux carrier PIN1 and the activity of the growth-repressor CUC2 (Bilsborough et al., 2011). In Brassicales, the species *A. thaliana* has simple leaves with margin protrusions at the base whereas *Cardamine hirsuta* produces dissected leaves divided into several leaflets. Similarly to leaf margin protrusions in *A. thaliana*, the formation of leaflets in *C. hirsuta* requires auxin maxima and the PIN1 protein (Barkoulas et al., 2008). However, the output of PIN1 action differs in that auxin induces growth of a limited number of cells at the *Arabidopsis* leaf margin, as opposed to induction of growth of the entire population of cells that will give rise to leaflets in *C. hirsuta*. The ability of PIN1 to promote leaflet formation involves regulation by KNOX proteins that are expressed in *C. hirsuta* leaves, but not in those of *A. thaliana* (Hay et al., 2006). Taken together, these findings suggest that differential auxin distribution is necessary to explain species-specific leaf shape in closely related species.

More recently, PIN1-mediated auxin activity maxima were shown to generate leaf dissection in tomato (Ben-Gera et al., 2012; Koenig et al., 2009), which unravels the molecular basis of the conversion from complex to simple leaves after treatment with PAT inhibitors in tomato (Avasarala et al., 1996) and pea (DeMason and Chawla, 2004). Moreover, KNOX proteins were shown to be required for leaflet formation in tomato (Bharathan et al., 2002). Given that dissected leaves evolved independently several times during the evolution of angiosperms, those findings suggest a broad role for auxin efflux in the elaboration of more complex leaf forms. KNOX/auxin interactions are similar to those operating in the SAM, suggesting that they may also be redeployed later in development of dissected leaves to generate leaflets. Nevertheless, further studies will be required to address the question whether changes in auxin biology are the cause or just a carrier of information due to changes in other regulators in natural variation.

Towards hypothetical models for body plan diversification

Very few differences in auxin-related gene content have been identified between lineages in land plants, suggesting that the core auxin machinery was already present in the last common ancestor of land plants. Thus, morphological innovations within land plants would be rather the result of evolutionary tinkering with the ancestral auxin regulatory network.

The recent identification of ER-localized PIN proteins in *Arabidopsis* (Mravec et al., 2009) has shed new light on the role of endoplasmic reticulum in auxin biology (Friml and Jones, 2010). Going further with this idea, we propose that changes in the trafficking of auxin-related proteins through the ER could have played a role in macroevolution. For example, ABP1 moss proteins differ from their homologs in flowering plants in that they lack the ER-retention motif KDEL and they are consequently not localized in the ER (Panigrahi et al., 2009). Another noteworthy point is that the moss genome does not contain amidohydrolases of the clade ILL1/ILL2/IAR3/ILL5/ILL6, whose members meet bioinformatics criteria for ER localization (Davies et al., 1999).

Changes in the coding region of proteins involved in nuclear auxin signaling could have also played a role in complicating the auxin regulatory network. The two huge ARF and Aux/IAA gene families mainly evolve by changes in coding regions, which can lead to the origin of truncated proteins. For example, some members of the ARF3/4 clade have lost their protein–protein interaction domains during the evolution of land plants, suggesting that they are not able to interact with Aux/IAA and are consequently insensitive to auxin (Finet et al., 2010a). Loss of these domains occurred several times during evolution and could represent a way to escape the auxin signaling pathway. Although relevant for ARF activators, this hypothesis seems unlikely for ARF repressors that have limited interaction with Aux/IAA proteins (Vernoux et al., 2011). Similarly, loss of functional domain I motif (LxLxL) that confers transcriptional repressor function of Aux/IAAs occurred independently several times during evolution of land plants (Paponov et al., 2009). However, the moss Aux/IAA proteins that contain the non-canonical motif LxLxPP may still interact with TPL (Causier et al., 2012), challenging the idea that loss of domain I motif LxLxL could affect Aux/IAA function.

Auxin is an instructive molecule that triggers a differential developmental output given its concentration. Thus, minor changes in auxin localization (e.g. mutations in promoters of biosynthesis genes, gain of novel tissue-specific enhancers) could have been responsible for important innovation at both micro- and macro-evolutionary scale.

From the embryogenetic point of view, roots are believed to have evolved from primitive shoots (Gifford and Foster, 1987). In *A. thaliana*, root- and shoot-specifying genetic pathways are tightly

linked since repression of root development module in the shoot is necessary for the proper shoot development (Long et al., 2006). Moreover, root stem cells establishment requires some shoot-specifying components (Grigg et al., 2009). Thus, it would be reasonable to imagine that changes (even minor) in auxin distribution, such as expansion in the basal part of the developing embryo, could have contributed to the emergence of roots.

Referring to the evolutionary conclusions brought by the study of *HOX* genes, Stephen Jay Gould liked to use the term 'hoxology'. It would be therefore timely to use the word 'auxology' to take into account the crucial role of auxin in plant evo-devo.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.ydbio.2012.05.039.

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