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REVIEWS

Plant Cell Proliferation and Its Regulators

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Abstract—Plant growth, where one of the key processes is cell division, is controlled by phytohormones. In this mini-review, an analysis of the literature on the molecular mechanisms controlling plant cell proliferation by phytohormones is presented.

Keywords: higher plants, phytohormones, cell proliferation, cell cycle

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INTRODUCTION

Unlike animals, plant growth occurring throughout the entire life of the plant organism is a continuous postembryonic process based on the cell division and an increase of cell sizes. However, with regard to plants more appropriate to consider not simply the regulation of cell division but to mean cell proliferation, including the control of the mitotic cycle itself, as well as a programmed cell cycle output and its subsequent reactivation. In fact, various types of the cell cycle (endomitosis, endoreduplication, etc.) together with both cell differentiation and death are the features that determine plant growth and development. These processes, being considered at the cellular level, should be associated with specific programs of plant development.

Disturbances in plant cell proliferation can have serious consequences, even though the plants are rather stable to changes at the level of cell cycle regulators. The study of genes encoding proteins that control the cell cycle, the role of phytohormones and their receptors, as well as hormone signal transduction pathways now acquired a significant extent. It became evident that a multicomponent regulatory system is responsible for the cell cycle progression, which includes controlled transcription, protein–protein interactions, phosphorylation/dephosphorylation, and protein degradation [1–3]. In this mini-review, an analysis of the literature on the molecular mechanisms controlling plant cell proliferation by phytohormones is presented.

Abbreviations: ACC—aminocyclopropan-1-carboxylic acid; BrdU—5-bromo-2'-deoxyuridine; CAK—CDF-activated kinase; CDK—cyclin-dependent protein kinase; CKI—CDK inhibitor; CPK—calcium-dependent protein kinase; CYC—cyclin; KRP—KIP (kinase inhibitory protein)-related protein; RBR—retinoblastoma-related protein; pre-RC—prereplicative complex; QC—quiscent center.

MECHANISMS OF CELL CYCLE REGULATION

Like in all other eukaryotes, plant cell division includes the phases of DNA replication and segregation: S-phase (S) and mitosis (M). Between them there are two gaps, G1 and G2: G1 is the interval time between M and S, whereas G2 – between S and M. In order each daughter cell received similar set of the inherited material, G1/S and G2/M transitions should be controlled. The main regulators of these transitions are Ser/Thr cyclin-dependent protein kinases (CDK), which are activated by binding to the regulatory proteins cyclins (CYC) (table).

In *Arabidopsis*, seven classes of CDK are distinguished (from A to G) on the basis of sequence similarities in domains of CYC binding [4]. In all eukaryotes, CDKA are the main regulators of G1/S and G2/M transitions (table); they have a conserved PSTAIRE CYC-binding motif [4, 5]. CDKB kinases, detected only in plants [6], bind CYC with a PPTA/TLRE motif and operate almost exclusively during G2/M transition [7]. The members of CDKD and CDKF classes are closer in their structure and functions to CDK-Activating protein Kinases CAK [5, 8]. So far, there is no information regarding sites of CDKE, CDKC, and CDKG functioning.

As distinct from CDK, cyclins operate essentially only in dividing cells, and their content changes during the cell cycle. In most CYCs, there is a sequence of 100 amino acid residues (cyclin box, C-box) required for binding to CDK and also a Destruction box (D-box) sequence determining a possibility of ubiquitination, which results in a rapid proteolytic CYC degradation [9].

As compared to animals possessing 13 CYC classes (A–L and T), the set of plant CYCs is less diverse; nevertheless, in *Arabidopsis*, there are 40 various CYCs [10]. Cyclins A and B are called as mitotic CYCs

(table), because the peak of their expression is observed during S/G2/M and G2/M transitions, respectively, when the functions of their partners are fulfilled by CDKA and CDKB [6]. Since molecules of CYCA and CYCB comprise D-box, it is clear that these cyclins are subjected to ubiquitin-dependent proteolysis [5, 10].

The main regulators of G1/S transition are CYCD with a LxCx(D/E) motif in their N-terminal region for binding with Retinoblastoma-Related (RBR) protein and PEST motif providing for degradation in proteasomes. Most often, CYCD partners are CDKA and CDKB [5, 6, 11].

For successive progression of the cell cycle, the active state of the CDK–CYC complexes is necessary. The activity of these complexes is controlled by a group of proteins with the common name CKI (CDK Inhibitor). Among them are ICKs (Interactor/Inhibitor of Cdc2 Kinase), which are evidently active during both G1/S and G2/M transitions, although their requirement for entering into S phase seems most likely. In addition, in *Arabidopsis* there are seven CKI proteins, which are named KRP (Kip-Related Protein) [12, 13]. Note that in the current literature, KRP and ICK names are used as synonyms. All KRPs are shown to inhibit kinase activities of the CYCD2–CDKA and CYCD2–CDKB complexes; the extent of inhibition depends on which of the seven individual KRP proteins is functioning. It seems likely that KRPs can function as negative regulators of both G1/S and G2/M transitions. However, taking into account differences in the degree of inactivation of kinases associated with CYCD2, it may be supposed that each KRP protein has its own functions in the regulation of CDK–CYC complex activity [6, 10, 14].

The activity of CDK–CYC complexes may be regulated by aforementioned CAK protein kinases, which activate CDKs by specific phosphorylation on the conserved Thr160 residue [15]. The essential role of CAK as the activator of CDK–CYC complexes is timed to the G1/S transition, but whether CAK function during G2/M transition is unclear [7, 16].

It is known that the functional activity of CDKs providing for G2/M transition is under the negative control of protein kinase WEE, whereas protein phosphatase CDC25 (from Cell Division Control) is a positive regulator [17]. In *Arabidopsis*, WEE1 kinase can phosphorylate Tyr15 in CDKA;1 and Tyr23/24 in CDKD;1, CDKD;2, and CDKD;3 [18]. These data are consistent with the observation of CDKA activity regulation by kinase WEE1 during G2/M transition.

For a long time, the attempts to find a full-size phosphatase responsible for the CDK-activating dephosphorylation during the initiation of G2/M transition were commenced [4, 6]. Nevertheless, in *Arabidopsis* and rice plants, proteins with only a catalytic domain were identified, which can in vitro activate the corresponding kinase [19]. However, genes encoding these proteins could not restore the phenotype of the *cdc25*$^-$ mutants of *Schizosaccharomyces pombe* [20].

Cyclin-dependent protein kinases (CDK) of *Arabidopsis* and cyclins controlling the cell cycle

Regulator	Member of family	Phase of the cell cycle
CDK		
A	1	G1/S and G2
B	1;1	G2/M
B	1;2	G2/M
B	2;1	G2
B	2;2	G2
Cyclins		
A	1;1/1;2	G1/S (G2/M)
A	2;1/2;2/2;3/2;4	G1/S (G2/M)
A	3;1/3;2/3;3/3;4	G1/S (G2/M)
B	1;1/1;2/1;3/1;4	G2 or G2/M
B	2;1/2;2/2;3/2;4	G2 or G2/M
B	3;1	G2 or G2/M
D	1;1	G0/G1/S
D	2;1	G0/G1/S
D	3;1/3;2/3;3	G0/G1/S
D	4;1/4;2	G2/M
D	5;1	G0/G1/S
D	6;1	G0/G1/S
D	7;1	G0/G1/S

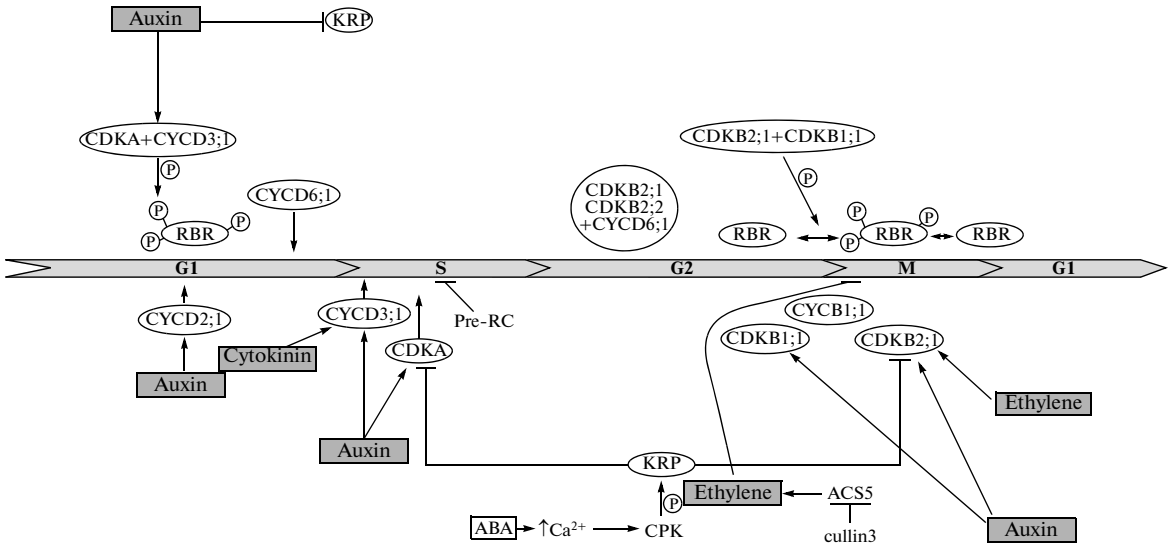
Of the considered data, it is evident that protein phosphorylation/dephosphorylation, consistent with the biochemical features of G1/S and G2/M transitions, is one of the most important mechanisms for the regulation of cell proliferation.

PHYTOHORMONES AS REGULATORS OF CELL PROLIFERATION

Through the traditional and novel experimental approaches, it was shown that extracellular and intracellular signaling molecules play a critical role in the regulation of cell division. Phytohormones are intracellular regulators, whose significance for proliferation is of no doubt. It was found that phytohormones are able to either directly determine the entry of cells into the cell cycle or operate through a variety of regulatory proteins.

Effects of Auxins and Cytokinins on Cell Proliferation

As positive regulators of cell division, auxins and cytokinins were studied in most details. It was found that these hormones exert unidirectional influence on



Major participants of the cell cycle regulation and points of their interactions with auxin, cytokinin, ABA, and ethylene.

the expression of many genes that serve the cell cycle [9, 21–24].

It was convincingly shown that auxin accumulation in the pericycle cells controls lateral root development via induction of cell division [25]. It was established that a substantial reduction in the number of lateral roots in the recessive mutants of *Arabidopsis* in the *CYCD4;1* gene can be restored by seedling treatment with auxin [26]. The enhanced expression of the *CYCD3;1* gene resulted in the activation of the auxin response and an increase in the lateral root density in the presence of 0.1 or 1.0 μM NAA [27]. At auxin-activated lateral root formation, expression of not only *CYCD3;1, CYCD6;1, CYCA2;4, CDKB2;1*, and *CDKB2;2* genes but also genes encoding proteins involved in the auxin signal transduction and auxin transport and synthesis were activated [27–29].

In *Arabidopsis* seedlings, cytokinins, like auxins, activated the expression of *CDKA, CYCD1;1, CYCD2;1,* and *CYCD3;1* genes but suppressed transcription of *KRP4* gene [23]. It was shown that the addition of zeatin to the cultivation medium of alfalfa protoplasts was required for the beginning of the S phase (figure), and this response to cytokinin was associated with the activation of CDKA1;1 and CDKB1;1. When cytokinin was not supplied, CDKA1;1 protein was synthesized, but its enzymatic activity, namely, a capability of histone H1 phosphorylation, was absent (figure). In contrast, G2/M kinases, CDKB1;1 for example, were functionally active in the absence of zeatin [30].

In the well-studied model system, in vitro cultivated tobacco BY2 cells, G2/M transition depends on the synthesis of zeatin and its riboside (figure). This fact was proved with the aid of lovastatin, which is often used as the cytokinin biosynthesis inhibitor, although its specificity is hardly high. In the BY2 cell culture, lovastatin not only suppressed cytokinin synthesis but also blocked G2/M transition. However, when BY2 cells were transformed with the *Spcdc25* gene from *S. pombe*, cell divisions occurred in the suspension culture in spite of the presence of lovastatin [31]. Based on the data described above, in BY2 cells expressing *Spcdc25* gene and treated with lovastatin, a general conclusion may be made: G2/M transition is functionally provided by cytokinin-regulated dephosphorylation of CDK protein.

Abscisic Acid as a Regulator of Cell Proliferation

ABA regulates plant growth and development via a signaling network, which functioning is sensitive to ABA level changing at various stresses [32]. Treatment of cultured BY2 cells with ABA blocked the cells at the boundary between G1 and S (figure) but evidently did not affect other phases of the cell cycle [33]. ABA as a negative regulator of cell division apparently operates by the suppression of expression of genes required for the initiation of DNA replication, for example *CDT1a*, encoding the component of the pre-replicative complex (pre-RC) [34], and also gene encoding topoisomerase I [35]. It should be emphasized that alfalfa leaf treatment with ABA suppressed CDK activity even in the presence of auxins and cytokinins [36].

There is considered that ABA, generated during abiotic stresses, inhibits plant growth by reducing the rate of cell division in roots and leaves. However, using antibodies against the PSTAIRE amino acid sequence, it was shown that the amount of Cdc2-like protein (CDK) did not change under drought conditions in the leaves of maize and wheat [37]. Remind that this conserved motif of binding to CYCs is present in CDKA, which regulate G1/S and G2/M transitions. On the other hand, in the roots of *Arabidopsis*

treated with 100 mM NaCl, the number of dividing cells decreased and there was a temporary drop in the CDK activity [38].

Lowered cell proliferation under stresses or after treatment with ABA may result from the enhanced expression of genes encoding the aforementioned inhibitors ICK/KRP [39]. Thus, it was shown that ICK1/KRP1 suppresses CDK activity [40–42]. When one considers that the expression of *ICK1* and *ICK2* is induced by ABA produced during stress [43], we can conclude that the functioning of the ABA signaling pathway that leads to the expression of *ICK/KRP*, whose activity is necessary for G0/G1/S transitions is the most logical way for a multilevel control of premature cell cycle triggering under unfavorable conditions. After passing S phase, ICK1/KRP can block cell cycle progression at the G2/M boundary (figure), which may lead to the endoreduplication. In *Arabidopsis*, KRP2 protein, regulating cell transition to endocycles, may serve a substrate for CDKB1;1; and its phosphorylation results in KRP2 destabilization [13]. In fact, the G2/M-kinase complexes are more sensitive to the recombinant inhibitor KRP of alfalfa cells than S-phase kinases [44]. However, above mentioned does not mean that the cells that have transited to the endoreduplication can not to come back into mitosis after the removal of a stress.

When discussing the ABA function as a regulator of cell proliferation, it is misleading to attribute to this phytohormone exclusively the role of inhibitor. This follows, in particular, from the study of *Arabidopsis ABA2/GIN1* gene. It was reported [45] that, in ABA-deficient mutants *aba2/gin1*, growth of cotyledons, rosettes, stems, roots, and pods was markedly retarded under non-stressful conditions and ABA treatment stimulated growth. It may be assumed that low ABA concentrations stimulate growth, but high concentrations retard it. In *aba2/gin1* mutants, small cotyledons are evidently developed because of the suppressed cell expansion, whereas small leaf rosettes are produced because of reduced number of cells and their smaller sizes; this implies that ABA influence on cell division during leaf development may be indirect [45]. Similar results were obtained for ABA-deficient mutants of tomato [46]. It is of interest that most mutants with the changed responses to treatment with sugars, which are required for correct seed germination and early seedling development, are associated with ABA functioning.

Ethylene: Stimulator or Inhibitor of Cell Proliferation?

In earlier studies contradictory data on the effect of ethylene on growth, which is provided by the ethylene-regulated cell division, were obtained. It was shown that ethylene inhibited DNA synthesis and also stimulated expression of genes encoding mitotic cyclins [21]. Recently it has been shown that ethylene most likely suppresses cell division (figure) through the inhibition of cytokinesis [47]. This effect turned out to be reversible, and after the removal of exogenous ethylene, cell division in the epidermis of cucumber hypocotyls was enhanced; as a result, multicellular trichomes and stomata with increased number of accompanying cells were produced [48].

The study of ethylene effect on DNA synthesis and cytokinesis in the epidermal cells of cucumber hypocotyls showed that, upon 24-h treatment with ethylene, the thymidine analogue 5-bromo-2'-deoxyuridine (BrdU) was detected in DNA of 20% of the epidermal cells, whereas BrdU did not essentially incorporate into DNA of untreated cells. The cytophotometric analysis of nuclei in cells treated with ethylene demonstrated an eight fold increase in the DNA content. However, during this time period, there were no signs of the cell plate formation. After ethylene removal, DNA content in the cells returned to the diploid level and new cell plates were produced. Thus, it was demonstrated that ethylene stimulated DNA synthesis but inhibited cytokinesis [47].

Although the inhibitory action of ethylene on root growth has long been known, only recently the data on the molecular mechanism underlying this process started to appear. Using the set of biochemical, genetic, and cellular approaches, it was shown that ethylene stimulated auxin biosynthesis in the roots via the activation of several genes of auxin biosynthesis. These gene turned out to be genes encoding α- and β-subunits of anthranylate synthase (ASA1), which catalyzes the first stage of auxin precursor, tryptophan, formation and also the genes encoding tryptophan aminotransferase (*TAA1*) and *TAR* (*TAA-Related*) [49, 50]. Auxin synthesized in the root meristem was then transported in the elongation zone. This process was controlled by ethylene and depended on the activities of the auxin carriers AUX1 and PIN2/EIR1 [51, 52].

In addition to the effect on elongation, ethylene can regulate cell division in the meristem. It was shown that, in the *eto1* mutant with ethylene overproduction, the number of cells in the quiescent center (QC) exceeded that in the wild type [53]. On the other hand, in response to ethylene treatment of ethylene-insensitive *ctr1* mutant, additional cells were produced in the QC [53]. Taking into account an important role of the QC in the meristem maintenance, it is reasonable to suppose that ethylene plays a key role in this process. It remains unclear whether this effect is a consequence of direct or auxin-mediated ethylene action. Treatment with auxin did not change the number of cell divisions in the QC; however, treatment with ethylene of some auxin mutants reduced a stimulatory effect of auxin [53]. This fact and also activation of *TAA1/TAR* gene expression in the meristem by ethylene [50] indicate that the effect of ethylene on the QC cells is mediated by auxin.

Thus, we concluded that ethylene, like auxin, can affect root growth by controlling cell division (figure). This idea is confirmed by experiments on *Arabidopsis* mutants with damaged *CULLIN3* gene [54]. An ubiq-

uitin-dependent ligase CULLIN3 (CUL3) is responsible for stability of 1-aminocyclopropan-1-carboxylic acid synthase (ACC5), e.g., the enzyme synthesizing an immediate precursor of ethylene (ACC). When CUL3 function was lost because of mutation, ACC5 remained stable and ethylene biosynthesis was activated. On the cellular level, this led to the reduction of the root meristem size and the number of cells in it. This conclusion was also confirmed in studies on mutants with a constitutively active response to ethylene, *ctr1* and *ebf1ebf2*, which root meristems were smaller than in the wild type. Therefore, it is reasonable to conclude that the cells can leave the meristem earlier and start to enlarge.

In above-discussed studies of the effects of phytohormones on cell proliferation, the authors used intact plants or their isolated organs. However, it should be kept in mind that in such objects dividing cells are localized only in certain structures and cell proliferation is controlled from the different centers, that brings about problems in the interpretation of data on the role of exogenous phytohormones. More appropriate model can be cultured plant cells, which represent a population of cells and can be treated with definite doses of compounds of interest. In fact, it was shown that suspension cultures of wild-type *Arabidopsis* and ethylene-insensitive mutants on *ETR1, CTR1*, and *EIN2* genes encoding, respectively, the ethylene receptor (ETR1) and the components of ethylene signal transduction pathways (CTR1 and EIN2) represent an adequate model not only for the studying the ethylene effect on cell division but also for the analysis of cross-talk with the pathways of other phytohormone signal transduction, ABA for example [55]. Thus, insensitivity to ethylene of mutants *etr1, ctr1*, and *ein2* resulted in a decrease in the number of dividing cells, indicating a necessity of sensitivity to ethylene for active in vitro division.

Intact *Arabidopsis* plants are characterized by mixoploidy [56]. This phenomenon is observed in the in vitro cultured cells as well. It turned out that the proportion of nuclei passed through three cycles of endoreduplication is higher in the *ctr1* cells with the constitutively active ethylene signal transduction pathway. In the presence of exogenous ABA, the biomass of wild-type cells decreased; in the *etr1* mutant, biomass was substantially increased; and in *ein2* mutant, there were no changes in growth activity. Since treatment with ABA lowered the decrease in the ethylene synthesis only in the wild-type cell culture and the proportion of living cells increased, it may be assumed that exogenous ABA maintained the ethylene biosynthesis at the level permitting cells to continue proliferation [55].

Thus, ethylene perception by the receptor (ETR1) and functioning of proteins transferring ethylene signal (CTR1 and EIN2) determine a capability of cultivated cells to proliferate actively, and ABA can correct this process.

On the basis of all above data, it becomes clear that all numerous elements involved in the regulation of cell proliferation may be the effectors of the phytohormone signal transduction pathways (figure). Apparently, one hormone can regulate cell division at different phases of the cell cycle. On the other hand, different phytohormones may affect the same phase of the cell cycle. Further studies will provide a framework, in which new molecular targets for phytohormones will be identified, and this will help to understand, which ones really are the components that regulate plant cell proliferation.

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