The EMBO Journal (2005) 24, 657–662 | © 2005 European Molecular Biology Organization | All Rights Reserved 0261-4189/05
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THE EMBO JOURNAL

New EMBO Member's Review

Green light for the cell cycle

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In recent years, considerable progress has been made in unraveling the control mechanisms operating on the plant cell cycle and most of the key regulators have now been identified, including cyclin-dependent kinases (CDKs), cyclins, CDK-inhibitory proteins, the WEE kinase and proteins of the retinoblastoma-related protein (RBR)/E2F/DP pathway. The review discusses recent developments in our understanding of the plant cell cycle machinery and highlights the role of the cell cycle in plant development.

The EMBO Journal (2005) **24,** 657–662. doi:10.1038/sj.emboj.7600561; Published online 27 January 2005
Subject Categories: cell cycle
Keywords: *Arabidopsis*; endoreduplication; plant cell cycle; plant cell differentiation; plant development

Introduction

The cell cycle is one of the most comprehensively studied biological processes, particularly given its importance for growth and development and in many human disorders. Research on yeast, worms, flies, frogs, mammals, and recently also plants, has contributed to a kind of universal picture on how the basic cell cycle machinery is regulated. However, much of this picture is based on experiments performed on single cells. It is surprising to note that the role of the cell cycle machinery during development has received relatively little attention. To understand how, in different organisms, the basic cell cycle machinery integrates with development is an important scientific challenge for the coming years. Plants offer exceptional opportunities to significantly contribute to such a challenge.

In contrast to animals, plant development is largely postembryonic. New organs, such as roots, stems, leaves and flowers, originate from life-long iterative cell divisions followed by cell growth and differentiation. Such cell divisions occur at specialized zones known as meristems. Leaves and flowers are formed at the shoot and floral meristems, respectively, whereas the root meristems continuously add new cells to the growing root. Plant development is also unique because any cell migration is prevented by the rigid cell walls surrounding plant cells. All these aspects make the analysis of the plant cell cycle of fundamental interest.

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Received: 16 September 2004; accepted: 29 December 2004; published online: 27 January 2005

The plant cell cycle

Cyclin-dependent kinases

Cyclin-dependent kinases (CDKs) govern, as in other eukaryotic organisms, the plant cell cycle. All eukaryotic organisms studied to date possess at least one CDK with the PSTAIRE hallmark. In plants too, a *bona fide* PSTAIRE CDK, designated CDKA, plays a pivotal role in both the G1/S and G2/M transitions. In agreement with a dual role in the cell cycle, overexpression of a dominant-negative *CDKA* completely abolishes cell cycle progression and arrests cells in both G1 and G2 (Hemerly *et al*, 1995; Joubès *et al*, 2004). No orthologs of the mammalian G1/S-specific *CDK4* and *CDK6* genes have been found in plant genomes to date. However, besides CDKA, plants contain a second, so-called B-type, class of CDKs that seem to be unique to plants. The PSTAIRE hallmark present in CDKAs is replaced by either PPTALRE or PPTTLRE, reflecting the existence of two subgroups, CDKB1 and CDKB2 (Vandepoele *et al*, 2002). CDKBs accumulate at the G2- and M-phase and are essential for regulating the G2/M transition (Magyar *et al*, 1997; Porceddu *et al*, 2001). Overexpression of a dominant-negative *CDKB* interferes with cell cycle progression and causes a G2 arrest (Porceddu *et al*, 2001; Boudolf *et al*, 2004a).

Cyclins

Plants contain many more cyclins than previously described in other organisms (Vandepoele *et al*, 2002; Wang *et al*, 2004). For example, despite its small genome size, *Arabidopsis thaliana* contains at least 32 cyclins with a putative role in cell cycle progression. The plant cyclin nomenclature is based on the functional similarity with the mammalian counterparts. *Arabidopsis* gene annotation identified 10 A, 11 B, 10 D and one H cyclins (Vandepoele *et al*, 2002; Wang *et al*, 2004). In a broad sense, D cyclins are thought to regulate the G1/S transition and appear to act as integrators of various signals; A cyclins are of importance for the S-to-M phase control; B cyclins generally play a role in the G2/M transition and intra-M phase control; and the H cyclin is part of the CDK-activating kinase. Although the complexity of plant cyclins can be attributed partly to extensive duplications of the *Arabidopsis* genome (Simillion *et al*, 2002), the large number of cyclins may reflect the high developmental plasticity of sessile plants to respond to both intrinsic developmental signals and environmental cues. The different cyclins may have a wide range of expression patterns and might confer different substrate specificities. Although much of this is speculation, the expression of plant cyclins, more specifically D cyclins, has been shown to be modulated by plant growth factors, such as cytokinins, brassinosteroids,

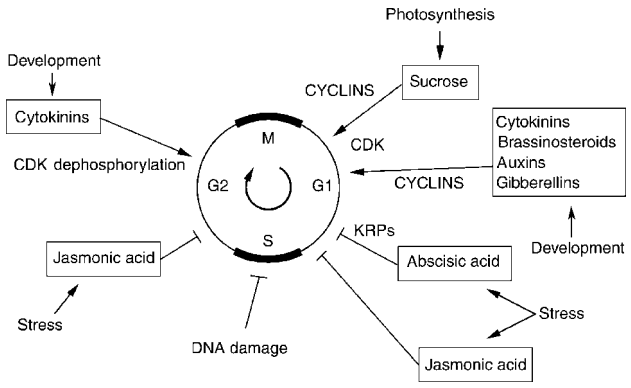

Figure 1 Schematic view of the various developmental and environmental signals that impinge on the plant cell cycle. For details, see text.

sucrose and gibberellins (Stals and Inzé, 2001). Figure 1 gives an overview of how developmental signals and environmental cues impinge on the cell cycle machinery. Some cyclins might act as key switches; for example, overexpression of *CYCD3;1* is sufficient to compensate for the lack of cytokinins in the culture medium (Riou-Khamlichi *et al*, 1999). However, the precise role of cyclins in the cell cycle, their stability throughout the cell cycle and their subcellular location are poorly understood.

Proteolysis

Plant cyclins are, as in other organisms, also subject to extensive regulation by proteolysis. B1 cyclins, a subclass of B cyclins, contain a destruction box and are a substrate for a ubiquitin-dependent protein ligase complex that strongly resembles the anaphase-promoting complex or APC/C (Criqui *et al*, 2000). The functional significance of this cyclin destruction is best exemplified by the observation that constitutive overexpression of a nondegradable B1 cyclin, lacking the destruction box, causes severe growth retardation and abnormal development, with a higher percentage of cells exhibiting duplicated ploidy levels than the controls (Weingartner *et al*, 2004). On the other hand, proteolysis of B2 cyclins at prometaphase appears to be proteosome independent (Weingartner *et al*, 2003). Recently, CYCD3;1, but not CYCD2;1, has been shown to be a highly unstable protein whose proteolysis is mediated by a proteasome-dependent pathway (Planchais *et al*, 2004). Other cell cycle regulators, such as CDC6 (Castellano *et al*, 2001) and E2Fc (del Pozo *et al*, 2002), are destroyed via the ubiquitin/26S proteasome pathway as well. With the exception of the apparent involvement of SKP2 in SCF-targeted proteolysis of E2Fc (del Pozo *et al*, 2002), it is currently unknown which of the 694 F-box proteins of *Arabidopsis* are involved in the specific recognition of the cell cycle regulatory proteins.

CDK phosphorylation

Similarly to that in yeasts and animals, the activity of plant CDK/cyclin complexes is regulated by phosphorylation/dephosphorylation and the interaction with regulatory proteins. Yeast CDK/cyclin complexes are subject to an inhibitory phosphorylation of an N-terminal Tyr residue in the CDK partner, whereas in vertebrates CDKs are phosphorylated on both an N-terminal Tyr and Thr residue. This phosphorylation is catalyzed by the WEE1 kinase and is counteracted by the dual-specificity phosphatase CDC25. Plants possess a WEE kinase, which is involved in the inhibitory phosphorylation of CDKAs (Sun *et al*, 1999; Sorrell *et al*, 2002; Vandepoele *et al*, 2002; our unpublished results). Recently, the primitive unicellular algae, *Ostreococcus tauri*, has been found to contain a *bona fide* CDC25 (Khadaroo *et al*, 2004). However, in both *Arabidopsis* and rice, no genes with high homology to yeast or animal *CDC25* genes have been identified (Vandepoele *et al*, 2002; our unpublished data). Nevertheless, both biochemical and genetic evidence suggest that higher plants too have a phosphatase that can activate CDK/cyclin complexes. Recently, a small protein with dual-specificity CDC25-like phosphatase has been identified in *Arabidopsis*. This CDC25-like protein consists of a sole catalytic domain and is able to stimulate *Arabidopsis* CDK activity (Landrieu *et al*, 2004). The *in vivo* role of this CDC25-like protein, however, remains to be determined.

CDK inhibitors

Plants also contain CDK/cyclin inhibitory proteins with a somewhat peculiar structure. All known plant CDK inhibitors share a 31-amino-acid domain with $p27^{Kip1}$, a member of the mammalian Kip/Cip family of CDK inhibitors. This conserved domain is essential for the interaction between CDKs and cyclins and is located in the N-terminus of the Kip/Cip proteins and in the C-terminus in the plant inhibitors (Wang *et al*, 1997; De Veylder *et al*, 2001). Based on this similarity, plant CDK inhibitors were designated Kip-Related Proteins (KRPs, De Veylder *et al*, 2001). KRPs interact with both CDKAs (but not CDKBs) and with D cyclins (Wang *et al*, 1998; De Veylder *et al*, 2001). The expression of *KRP* genes is consistent with a role in regulating the cell cycle during development and in response to environmental signals. For example, auxins trigger the re-entry of quiescent root pericycle cells into the cell cycle and this event is preceded by a very specific downregulation of *KRP2* gene expression in the auxin-responsive pericycle cells (Himanen *et al*, 2002). Furthermore, *KRP1* was upregulated by abscisic acid, a plant hormone implicated in stress-induced cell cycle arrest (Wang *et al*, 1998). No plant homologs to the INK4 family of inhibitors have been found (Vandepoele *et al*, 2002).

The RB/E2F/DP pathway

It is astonishing to observe that, despite one billion years of evolution separating animals and plants, both types of organisms use the same RB/E2F/DP pathway to control the G1/S transition. Even the canonical DNA sequence (TTTCCCGC) recognized by the E2F transcription factors of animals and plants is identical (Ramirez-Parra and Gutierrez, 2000; de Jager *et al*, 2001). This identity argues in favor of the hypothesis that the RB/E2F/DP pathway had already evolved in primitive organisms, before the branching between animal and plant taxa. On the other hand, this well-studied pathway does not occur as such in yeasts and has long been thought to be specific for multicellular organisms. However, this idea has been challenged by the discovery of a retinoblastoma-related protein (RBR) in the unicellular green flagellate *Chlamydomonas reinhardtii* (Umen and Goodenough, 2001) and the recent identification in yeast of Whi5, an inhibitor of G1-specific transcription that is antagonized by Cln/CDK activity (Costanzo *et al*, 2004; de Bruin *et al*, 2004).

As their animal counterparts, all known plant RBR proteins contain two blocks of conserved sequences, which form the so-called A/B pocket domain. This pocket domain is the docking place for the E2F transcription factors. Plant RBR proteins interact with D cyclins through a conserved LXCXE motif at the N-terminus of the latter (Huntley *et al*, 1998). Recently, a loss-of-function of the *Arabidopsis RBR* gene has been shown to be gametophytically lethal (Ebel *et al*, 2004).

Arabidopsis has six E2Fs (E2Fa, E2Fb, E2Fc, E2Fd/DEL2, E2Fe/DEL1 and E2Ff/DEL3) and two DPs (Vandepoele *et al*, 2002). Two of the E2Fs (E2Fa and E2Fb) act as activators and E2Fc as repressor (del Pozo *et al*, 2002; Kosugi and Ohashi, 2002; Mariconti *et al*, 2002; Rossignol *et al*, 2002). Overexpression of *E2Fa/DPa* or *E2Fb/DPa* shortens cell cycle duration (unpublished data). E2Fa, E2Fb, E2Fc and DPs only contain one DNA-binding domain and, therefore, require dimerization to interact with the canonical E2F motif. On the other hand, E2Fd/DEL2, E2Fe/DEL1 and E2Ff/DEL3 proteins contain two DNA-binding domains, allowing them to bind as a monomer to the E2F site (Kosugi and Ohashi, 2002; Mariconti *et al*, 2002; Vandepoele *et al*, 2002). Additionally, these proteins do not contain a transactivation domain. Interestingly, only very recently a mammalian homolog, designated E2F7, has been discovered in mammals (reviewed by Bracken *et al*, 2004). This discovery highlights that cell cycle research in plants can yield novel insights into cell cycle research in animals. E2F proteins with two DNA-binding motifs act as competitors of *bona fide* E2F/DP proteins and, because they lack an activation domain, they repress E2F/DP-regulated genes (Mariconti *et al*, 2002; Bracken *et al*, 2004). Recently, E2Ff/DEL3 has been shown to play a possible role in repressing cell wall biosynthesis during cell elongation in differentiated cells (Ramirez-Parra *et al*, 2004) and E2Fe/DEL1 appears to control endoreduplication (Vlieghe *et al*, 2005).

Cell cycle and development

The role of the cell cycle machinery in plant development has been subject to a great deal of debate. Obviously, division is essential in generating the cells that constitute tissues and organs. However, the question whether cell division is the driver of growth and development (known as the cellular theory) or, alternatively, merely follows a developmental plan (known as the organismal theory) is more difficult to answer. Thanks to the ability to alter cell cycle parameters in transgenic plants, this long-standing question has been addressed. At least for leaves, development seems to follow the concept laid down in the organismal theory. In other words, the size and shape of leaves is, to some extent, predetermined and cell division merely serves to fill the predetermined space by cells. Experimental data support this viewpoint: transgenic plants constitutively overproducing any of the CDK inhibitors (KRPs) have smaller leaves that consist of 10-fold fewer cells whose average size is six-fold greater than that of control cells (Figure 2A–D). The reduction in cell number is thus compensated by an increased cell size (Wang *et al*, 2000; De Veylder *et al*, 2001; Jasinski *et al*, 2002). Similarly, overexpression of a dominant-negative *CDKA* or a nondegradable *CYCB1;1* in tobacco retards the cell cycle and causes the formation of larger cells (Hemerly *et al*, 1995; Weingartner *et al*, 2004). On the other hand, constitutive overexpression of positive regulators of the cell cycle, such as *E2Fa* or *CYCD3;1*, results in more smaller cells (De Veylder *et al*, 2002; Dewitte *et al*, 2003; Figure 2E–H). Again, an increase in cell number is compensated by a decrease in cell size. Plants overexpressing *E2Fa* have larger cotyledons (leaf-like structures formed in the developing embryo) with three-fold more cells that are approximately twice as small as the control cells (De Veylder *et al*, 2002). Transgenic plants overexpressing *CYCD3;1* show a massive increase in cell proliferation, which is, to some extent, balanced by a decrease in cell size (Dewitte *et al*, 2003). Also in animals, cell division and cell expansion can compensate each other to achieve an optimal species-specific organ size (Potter and Xu, 2001).

Evidence also suggests that cell division acts independently of cell differentiation. Neither inhibition (by using, for instance, dominant-negative CDKs or KRPs) nor stimulation (by using overexpression of *CYCB1;1*, *CYCD2;1*, *CYCD3;1* or *EFa/DPa*) severely affect cell differentiation (Hemerly *et al*, 1995, 2000; Doerner *et al*, 1996; Cockcroft *et al*, 2000; De Veylder *et al*, 2001, 2002). For example, trichome-specific expression of *CYCD3;1* in *Arabidopsis* converts unicellular trichomes (leaf hairs) in multicellular hairs, without affecting differentiation (Figure 2I–J; Schnittger *et al*, 2002). Another example highlighting the independence of cell division from cell differentiation is found in transgenic *Arabidopsis* plants expressing a dominant-negative *CDKB1;1*. In these plants, many stomata, normally built of two guard cells, consist of only one kidney-shaped cell (Figure 2K–L; Boudolf *et al*, 2004a).

Endoreduplication

The normal cell cycle mode is characterized by a round of DNA replication (S phase) followed by mitosis and cytokinesis (M phase) and separated by two gap phases (G1 and G2). However, many plant and animal cells have a different cell cycle mode in which cells undergo iterative DNA replications without any subsequent mitosis and cytokinesis. This endoreduplication is frequently observed in some, but not all, plants and the level of ploidy varies between species and tissues (Sugimoto-Shirasu and Roberts, 2003). The physiological role of endoreduplication is subject to debate and several hypotheses have been proposed. For a long time, endoreduplication has been believed to be essential to allow cell growth and to maintain an optimal balance between cell volume and nuclear DNA. However, this concept is currently challenged. First, cell size and ploidy level are not correlated in root cells of different *Arabidopsis* ecotypes (Beemster *et al*, 2002). Secondly, recent experiments in which the level of endoreduplication is modified also do not support this hypothesis. For example, overproduction of KRPs causes a remarkable overall decrease in ploidy level but, at the same time, a large increase in cell size (De Veylder *et al*, 2001; Jasinski *et al*, 2002; Zhou *et al*, 2002). Alternatively, endoreduplication might buffer mutations that plants accumulate during their sessile life. Indeed, many plants are exposed during their life cycle to less favorable conditions and having 8, 16, 32, 64,… copies of the genome would safeguard that the genome retains functional copies. To our knowledge, no experimental data support this hypothesis, but available transgenic plants in which the ploidy level is changed might address this question experimentally. Furthermore,

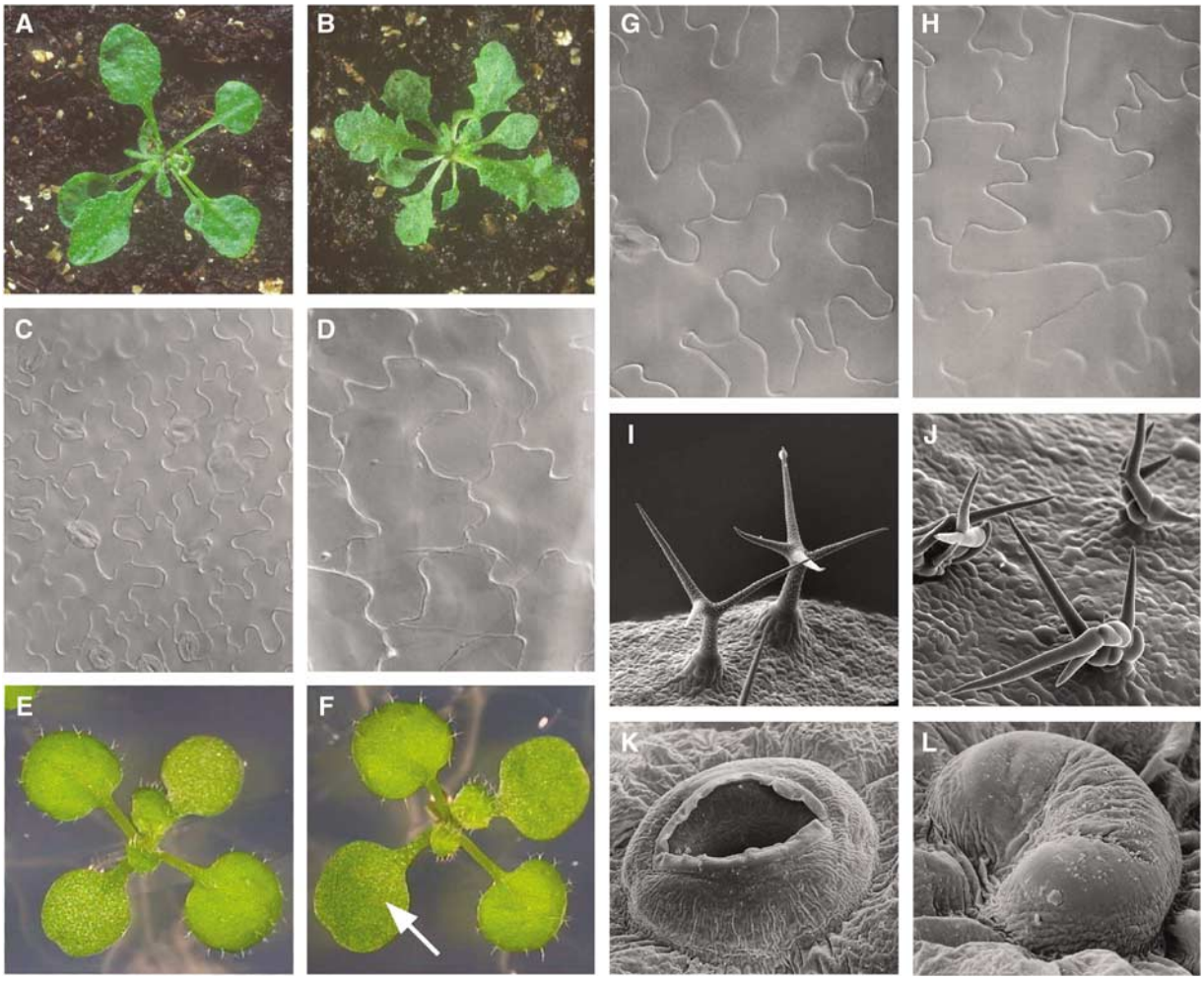

Figure 2 Examples of phenotypes caused by ectopic overexpression of cell cycle genes. (**A, C, E, G, I, K**) Wild-type plants and structures. (**B, D**) Plants constitutively overexpressing *KRP2*, a CDK inhibitor. Note the serrated leaves (B) composed of fewer, but much larger cells (D) (De Veylder *et al*, 2001; © 2001, American Society of Plant Biologists, reprinted with permission). (**F, H**) Overexpression of *E2Fa* leading to the formation of larger cotyledons (F, arrow), consisting of a larger number of cells with a smaller average size (H) (De Veylder *et al*, 2002). (**J**) Trichome-specific overexpression of *CYCD3;1* causing the formation of multicellular hairs, whereas the wild-type hairs are unicellular (I) (Schnittger *et al*, 2002; © 2002, National Academy of Sciences, USA, reprinted with permission). (**L**) Constitutive overexpression of a dominant-negative *CDKB1;1* interfering with the development of stomata. Whereas the wild-type stomata are built of two guard cells (K), the transgenic stomata often consist of only one kidney-shaped cell (L) (Boudolf *et al*, 2004a; © 2004, American Society of Plant Biologists, reprinted with permission).

a hypothesis states that endoreduplication might enhance the metabolic capacity of plant cells. The endosperm cells of cereal seeds are highly polyploid and, possibly, the numerous gene copies allow these cells to synthesize very large amounts of storage products, such as starch. However, transgenic maize endosperm producing a dominant-negative form of CDKA had a lower level of endoreduplication, but only a slightly reduced starch and storage protein accumulation (Leiva-Neto *et al*, 2004).

How are cells triggered to undergo endoreduplication? In maize endosperm and tomato fruit development, the onset of endoreduplication coincides with the inhibition of a M-phase-specific CDK by a yet unknown factor (Sugimoto-Shirasu and Roberts, 2003). The best documented molecular mitosis-to-endocycle switch is the CCS52A protein, a plant ortholog of the yeast and animal CDH1 proteins that acts as a substrate-specific activator of the APC/C. Mitotic cyclins are likely candidate substrates of CCS52A-mediated proteolysis (Kondorosi and Kondorosi, 2004). The recent finding that CDKB1;1 also plays an important role in the decision between mitosis and endocycle makes it also a possible CCS52A substrate (Boudolf *et al*, 2004b).

Perspectives

Plants, particularly *Arabidopsis,* will help considerably in gaining a better understanding of the relationship between cell cycle and developmental signals as well as environmental cues. Nowadays, the generation of transgenic plants is very simple and can easily be done high throughput, thus allowing the testing of many genes for function, expression and localization of the corresponding proteins. Furthermore, plants have an astonishing developmental plasticity and, despite the dramatic effect of some cell cycle perturbations, seed set can often be obtained. All these factors call for a green light to further endorse research on the plant cell cycle.

Acknowledgements

I sincerely thank all past and current members of the plant growth and development group of the Department of Plant Systems Biology for their continuous efforts to unravel the plant cell cycle. I am particularly grateful to Lieven De Veylder, Ryan Whitford and Tom Beeckman for their suggestions to improve this review and to Martine De Cock, Karel Spruyt and Hilde Diegenant for helping preparing the manuscript.

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