Novel roles of plant RETINOBLASTOMA-RELATED (RBR) protein in cell proliferation and asymmetric cell division

Bénédicte Desvoyes1,*, Alex de Mendoza2,3, Iñaki Ruiz-Trillo2,3 and Crisanto Gutierrez1,*

1 Centro de Biología Molecular Severo Ochoa, CSIC-UAM, Cantoblanco, Nicolas Cabrera 1, 28049 Madrid, Spain
2 Institut de Biologia Evolutiva (CSIC-Universitat Pompeu Fabra), Passeig Marítim de la Barceloneta 37–49, 08003 Barcelona, Spain
3 Institució Catalana de Recerca i Estudis Avançats (ICREA), Passeig Lluís Companys 23, 08010 Barcelona, Catalonia, Spain

* To whom correspondence should be addressed. E-mail: bdesvoyes@cbm.csic.es and cgutierrez@cbm.csic.es

Received 27 September 2013; Revised 5 November 2013; Accepted 7 November 2013

Abstract

The retinoblastoma (Rb) protein was identified as a human tumour suppressor protein that controls various stages of cell proliferation through the interaction with members of the E2F family of transcription factors. It was originally thought to be specific to animals but plants contain homologues of Rb, called RETINOBLASTOMA-RELATED (RBR). In fact, the Rb–E2F module seems to be a very early acquisition of eukaryotes. The activity of RBR depends on phosphorylation of certain amino acid residues, which in most cases are well conserved between plant and animal proteins. In addition to its role in cell-cycle progression, RBR has been shown to participate in various cellular processes such as endoreplication, transcriptional regulation, chromatin remodelling, cell growth, stem cell biology, and differentiation. Here, we discuss the most recent advances to define the role of RBR in cell proliferation and asymmetric cell division. These and other reports clearly support the idea that RBR is used as a landing platform of a plethora of cellular proteins and complexes to control various aspects of cell physiology and plant development.

Key words: Arabidopsis, asymmetric cell division, cell cycle, gene expression, phosphorylation, plant, Rb phylogenetic tree, retinoblastoma-related (RBR).

Historical and evolutionary overview

Cell-cycle research witnessed a series of key discoveries about 20–25 years ago. Studies in yeast and later in mammalian cells indicated that the G1/S and the G2/M transitions were the major points controlling cell-cycle progression. However, except for the involvement of the Cdc2 kinase required for both the G1/S and the G2/M transitions in fission yeast (Nurse and Bissett, 1981), the molecular framework for these transitions was virtually unknown, in particular in higher eukaryotes. The finding that, in the vast majority of human tumours, the product of the retinoblastoma (Rb) gene was inactivated (Knudsen and Knudsen, 2006) and the identification and cloning of the human Rb gene constituted major breakthrough discoveries in mammalian cell-cycle research (Friend et al., 1986; Fung et al., 1987; Lee et al., 1987). Soon afterwards, the pivotal roles of Rb as a tumour suppressor, as a negative regulator of the G1/S transition and as a modulator of the switch from quiescence to proliferation, were definitely established (Weinberg, 1995; Manning and Dyson, 2012). All these functions rely largely on the interaction of Rb protein with transcription factors (e.g. members of the E2F family, and with CDK/cyclin complexes, in particular CycD-containing complexes). These proteins bind to Rb through the LxCxE amino acid motif present in CycD. This leads to the phosphorylation and inactivation of Rb, which no longer binds to E2F, thus allowing the expression of E2F targets required for G1/S progression. This normal regulatory circuit can be bypassed by DNA tumour viruses that encode proteins, such as SV40 T-ag or HPV E7, that bind Rb through their LxCxE motifs, mimicking binding of CycD to Rb, inactivating it, and stimulating cell-cycle progression (DeCaprio, 2009).
Nowadays, it is clear that the general principles governing cell-cycle progression are largely conserved in all eukaryotes, including plants. However, back in the early 1990s and based on (i) the absence of Rb in yeast, (ii) the similarity of the first CDK and cyclins identified in plants to yeast proteins, and (iii) the rather naïve assumption that plant cells ‘must’ have a simple and primitive cell-cycle regulatory circuitry, it was widely accepted that the Rb–E2F pathway was an animal invention.

Two major lines of research provided new insights that changed the view on plant cell-cycle regulation. One was the finding that plants contain homologues of the D-type cyclins (Dahl et al., 1995; Soni et al., 1995). Although D-type cyclin phylogenetic relationships are not well resolved (Ma et al., 2013) and the degree of similarity of plant CYCD with human proteins is very limited, they share structural and functional similarities, such as their expression patterns and, most remarkably, a LxCxE amino acid motif (Soni et al., 1995; Huntley et al., 1998; Murray et al., 1998; Riou-Khamlichi et al., 1999). Another strongly provocative finding came from the field of geminiviruses, a rather unique family of plant DNA viruses. Replication of the virus genome occurs within the nucleus of the infected cell through double-stranded DNA intermediates that are the transcriptionally active templates (reviewed in Gutierrez, 2000; Gutierrez et al., 2002; Jeske, 2009). Interestingly, geminiviruses also trigger nuclear DNA synthesis (Nagar et al., 1995; Hanley-Bowdoin et al., 2000). Remarkably, the early RepA protein of wheat dwarf virus (WDV) contains a LxCxE amino acid motif that is functionally active since it mediates heterologous interaction of RepA with human Rb protein and when mutated reduces significantly virus DNA accumulation in cultured plant cells (Xie et al., 1995; Gutierrez, 2000).

Together, this circumstantial evidence strongly suggested that the Rb pathway might not be a novel and unique acquisition of animals but instead an ancient invention shared with plants. Indeed, early studies based on the identification of expressed sequence tag sequences of maize showed that the RBR–E2F pathway has been shown to have roles in cell proliferation, endoreplication, differentiation, and stem cell biology among other aspects of plant physiology. These have been discussed in other recent comprehensive reviews on the role of RBR during plant development (Dudits et al., 2011; Gutzat et al., 2012) and on the regulatory function of mammalian Rb (Chinnam and Goodrich, 2011; Henley and Dick, 2012; see also Kuwabara and Gruissem, in press, this issue). Here, we will focus on recent findings not reviewed so far in the context of plant cell cycle and development.

**Regulation of RBR expression**

The RBR promoter contains E2F-binding sites. Consistent with this, its expression is cell-cycle regulated and peaks at G1 in synchronized cell cultures (Menges et al., 2005). Nevertheless, the regulation of RBR expression by other transcription factors involved in different programmes of differentiation has been also reported. Trichome initiation requires the R2-R3 MYB GLABRA1 (GL1) and the bHLH GLABRA3 (GL3) or ENHANCER OF GLABRA 3 (EGL3) transcription factors to control the expression of specific epidermal cell fate genes (Schellmann and Hulskamp, 2005). Moreover, this GL1/GL3 complex binds to the promoter (DP) proteins were identified (Ramirez-Parra et al., 1999; Magyar et al., 2000; Ramirez-Parra and Gutierrez, 2000; Kosugi and Ohashi, 2002; Mariconti et al., 2002; Vlieghe et al., 2005). All these data obtained from both animal and plant cells supported the idea that the presence of the RBR–E2F pathway might be linked to the explosion of multicellular forms of life about 800–1000 Mya. However, RBR was identified as well in some unicellular algae, such as Chlamydomonas reinhardtii and Ostreococcus tauri (Umen and Goodenough, 2001; Moulager et al., 2010). It was also identified in colonial algae, such as Volvox (Kianianmomenti et al., 2008), and in many other eukaryotes, underscoring the ancient origin of the RBR gene. In fact, at least one species of each of the eukaryotic supergroups has a Rb gene. Interestingly, E2F genes are also present (Fig. 1) in taxa with a Rb gene, except for the ciliated fungi Batrachochytrium dendrobatidis. It is worth noting that some species have secondarily lost both RBR and E2F genes, e.g. yeast, whereas others have lost just the Rb gene. In the particular case of plants and green algae (Viridiplantae), in agreement with other studies (Gutzat et al., 2012), all the taxa analysed have at least one RBR gene (except the Glaucochyta) and several E2F genes (Fig. 1). Thus, it is clear that the plant ancestor already had the RBR–E2F module. Indeed, the presence of both RBR and E2F genes in the genomes of animals and other eukaryotic lineages, including excavates, amoebozoans, and apusozoans indicates that the RBR–E2F pathway appeared before the divergence of the plant and animal lineages, most likely in the Last Eukaryotic Common Ancestor (Roger and Simpson, 2009; Cao et al., 2010; Cross et al., 2011; Derelle and Lang, 2012).

The decade after the discovery of RBR in plants served to demonstrate unequivocally that RBR is more than just part of the cell-cycle machinery (Gutierrez, 2005). Thus, the RBR–E2F pathway has been shown to have roles in cell proliferation, endoreplication, differentiation, and stem cell biology among other aspects of plant physiology. These have been discussed in other recent comprehensive reviews on the role of RBR during plant development (Dudits et al., 2011; Gutzat et al., 2012) and on the regulatory function of mammalian Rb (Chinnam and Goodrich, 2011; Henley and Dick, 2012; see also Kuwabara and Gruissem, in press, this issue). Here, we will focus on recent findings not reviewed so far in the context of plant cell cycle and development.
and activates the expression of RBR and the protein kinase inhibitor SIAMESE (SIM) (Morohashi and Grotewold, 2009), suggesting that this transcription factor complex contributes directly on the expression of cell-cycle genes in the trichome precursor cell to control trichome development and endoreplication programme associated with it. Accordingly, the GL3 mutant allele shapeshifter (gl3-sst) that is no longer able to bind GL1 presents an extremely enhanced endoreplication phenotype in trichomes (Esch et al., 2003) that could be due to the lack of GL1/GL3-controlled RBR expression to terminate the endoreplication programme. Furthermore, the presence of E2F-binding sites in the 3′-untranscribed region of GL1 mRNA, essential for gene expression, suggests a possible negative feedback regulation of the RBR/E2F pathway on GL1 expression (Wenger and Marks, 2008).

A second example of regulation of RBR during specific development programmes concerns TCP15, a member of the class I TCP transcription factor family (TEOSINTE BRANCHED 1 CYCLOIDEA), and TCP14, which have redundant roles in promoting cell proliferation in the young internodes while repressing it in the developing leaves (Kieffer et al., 2011). TCP15 regulates the expression of several cell-cycle genes, including RBR, and binds directly to the RBR promoter at the TCP-binding sites and activates its transcription (Li et al., 2012).

These two examples suggest an important role of RBR in controlling the cell cycle during specific developmental programmes, and an attractive hypothesis is to consider RBR as an effector of specific transcription factors to coordinate proliferation/differentiation programmes. These data shed light on the complexity of the regulation of cell proliferation and endoreplication programmes in a context of organ formation.

**Structure of the retinoblastoma protein**

All of the structural information available in the literature comes from studies on the human Rb protein (Fig. 2). Rb is a phosphoprotein that contains two highly structured domains, each with a tandem cyclin fold known to mediate protein–protein interactions. One is located at the N-terminus (Rb-N) and another in the central domain (AB or small pocket) (Lee et al., 1998; Hassler et al., 2007; Balog et al., 2011). Rb also contains several highly disordered sequences between the structured domains and at the C-terminus, and it is in these sequences that reside most of the phosphorylation sites (Rubin et al., 2005).

Crystallographic studies of individual domains with or without interacting peptides identified the LxCxE-binding motif in a groove of the B pocket (Lee et al., 1998; Hassler et al., 2007; Balog et al., 2011). Binding of E2F is more complex and requires the large pocket formed by the AB pocket (Rb-AB) and the C-terminal domain (Rb-C). The marked box of E2F and DP heterodimers binds to the flexible Rb-C and is modulated by phosphorylation of Ser/Thr residues on Rb-C (Rubin et al., 2005). Recently, structural and calorimetric studies on phosphorylated forms of Rb shed light on the precise mechanism of E2F release upon phosphorylation. Residue S608 is located in the spacer located between A and B pocket domain.
where the E2F transactivation domain (E2F\textsuperscript{TD}) binds. When this residue is phosphorylated, the unstructured sequence binds to the pocket interface and the interaction with E2F\textsuperscript{TD} is competitively inhibited. A second phosphorylation event at T373 located in the unstructured region between Rb-N and Rb-AB provokes a major conformational change docking Rb-N and Rb-AB. This converts the elongated architecture of the protein into a globular compact conformation, thus releasing E2F and LxCxE-containing proteins (Burke et al., 2010; Burke et al., 2012; Lamber et al., 2013). Since plant RBRs present a significant sequence similarity and share the same domain organization with their mammalian counterparts (Fig. 2) it is conceivable that many structural features are also shared between animal and plant Rb proteins.

Multiple interactors of Rb have been identified (Morris and Dyson, 2001; Goodrich, 2006) Thus, an emerging idea is that Rb acts like a platform to bring different cellular proteins and enzymic activities to a specific chromatin location (Chinnam and Goodrich, 2011; Munro et al., 2012). Sequential phosphorylation by cyclin/CDK complexes, according to a phosphorylation code that still needs to be uncovered, modulates the binding to different partners (Rubin, 2013). All this structural knowledge gathered for Rb constitutes valuable information to characterize the function of plant RBR partners, although the current list of known RBR partners is not as wide as that for human Rb.

**Cell-cycle and endocycle regulation**

One of the key points of cell-cycle regulation is the G1/S transition, where cells take the decision to initiate a new round of DNA replication. In animal cells, the role of Rb as a negative regulator of the E2F transcription factor family and recruiting co-repressors proteins is now well established (Henley and Dick, 2012). Upon external stimuli, Rb is inactivated by Cyc/CDK-mediated phosphorylation, released from E2F/DP complexes, and transcription of E2F targets is activated to initiate S phase (Chinnam and Goodrich, 2011). Plant cells frequently exit the cell cycle and switch to the endoreplication cycle whereby cells undergo successive full genome replication rounds in the absence of mitosis. The RBR/E2F pathway is conserved in plants and participate both in cell-cycle regulation and endoreplication onset (Fig. 3)(Gutiérrez, 2009). Since rbr loss-of-function mutants are gametophytic lethal (Ebel et al., 2004), several strategies,
such as viral-induced gene silencing, inactivation of RBR by viral proteins, or inducible RNAi, have been designed to circumvent this experimental drawback. Conditional inactivation of RBR leads to an activation of both mitotic and endoreplication cycles that depend on the stage of plant development at the time of inactivation of RBR (Park et al., 2005; Desvoyes et al., 2006; Jordan et al., 2007), a phenotype reminiscent to that of plants overexpressing E2Fa/DPa (De Veylder et al., 2002). Downregulation of RBR within a window when proliferation has not yet ceased leads to localized hyperproliferation. This suggests that only cells competent for cell division respond in that way to RBR inactivation (Park et al., 2005; Desvoyes et al., 2006; Borghi et al., 2010). In leaves, responsive cells express TMM, a meristemoid marker, indicating that the cells that proliferate are of the stomatal lineage (Borghi et al., 2010). These are indeed known to be the last to exit the cell cycle during leaf development (Gonzalez et al., 2012). Although RBR inactivation in cells that already exit mitotic cycle will trigger endoreplication (Park et al., 2005; Desvoyes et al., 2006; Jordan et al., 2007), RBR overexpression in its own domain of expression had the opposite effect and represses both cell proliferation and endoreplication (Magyar et al., 2012). The maize genome possesses four different RBR genes, which can be separated in two different types: RBR1 and RBR2, and RBR3 and RBR4 (Sabelli and Larkins, 2006). RBR1 is the orthologue of Rb, whereas RBR3 shows more similarity to the mammalian p107 (Sabelli et al., 2005). RBR3 is a target of the RBR1/2E2 pathway and positively regulates the expression of replication genes (Sabelli et al., 2009). Recently, it has been shown that RBR1 regulates cell proliferation, endoreplication, and cell death during endosperm development (Sabelli et al., 2013). These phenotypes are reminiscent of the effect of E2Fa-DPa overexpression that also has this dual effect on the mitotic and endocyte (De Veylder et al., 2002; Kosugi and Ohashi, 2003; Magyar et al., 2012). The well-established model of RBR/E2F pathway G1/S regulation was recently questioned by a surprising report regarding this dual role of RBR/E2Fa (Magyar et al., 2012). Quantitative immunoprecipitation experiments showed that, in proliferative cells, RBR–E2Fa, but not RBR–E2Fb, forms a stable repressive complex that is resistant to phosphorylation in conditions where CYCD3;1 activity is high. Interestingly, a stable RBR–E2F complex has been also identified in Chlamydomonas (Olson et al., 2010). RBR–E2Fa complexes, together with the atypical E2F DEL1/E2Fe, repress the APC activator and endocycle-promoting genes CCS52A, thus, maintaining cell proliferation status (Lammens et al., 2008; Magyar et al., 2012). The authors suggest that the classic G1/S transition mediated by phosphorylation of RBR during mitotic cycle targets RBR–E2Fb complexes. In differentiating cells, E2Fa is released from RBR, by an unknown mechanism triggering the expression of genes, such as CCS52, which will activate endoreplication. This pathway may need the coordinated phosphorylation at other sites on RBR by CDK associated with cyclins other than CYCD3;1. This mechanism can be similar to that found in mammalian cells where Rb/E2F1 complexes, resistant to CDK phosphorylation and present during S phase, have been also reported (Henley and Dick, 2012).

Since RBR function is strictly dependent on its phosphorylation level by CDK, the status of CDK inhibitors emerges as an important component. In fact, a new layer of complexity in the regulation of the G1/S transition has been recently reported and involves the key role of proteasome degradation of members of the KIP-related CDK inhibitors family (KRP). The F-Box protein (FBL17) forms cullin 1-containing E3 ubiquitin ligase complex (SCF-FBL17) that targets KRP6 and KRP7 for degradation, an essential step for the proliferation of male germ cells (Kim et al., 2008; Gusti et al., 2009) but also required for the female gamete development (Zhao et al., 2012). The fbl17 mutant resembles edka loss-of-function alleles in that pollen fails to progress through the mitotic division (Kim et al., 2008; Gusti et al., 2009). Interestingly, FBL17 was identified as an E2F target gene (Vandepoele et al., 2005). It is upregulated in plants overexpressing E2Fa/DPa (Gusti et al., 2009) and regulated directly by E2Fa and RBR (Zhao et al., 2012). The regulation cascade involves four steps of negative regulation and forms a loop where FBL17 inhibits CDKA;1 that in turn inhibits RBR by phosphorylation that inhibits E2Fa that, finally, controls FBL17 and other replication genes’ expression. The negative feedback wiring favours the hysteresis finely controlling the switch to S phase (Zhao et al., 2012). FBL17 is widely expressed in different plant organs (Kim et al., 2008) and mediates the degradation of different members of the KRP family, suggesting a more general role in regulating the entry into S phase not only limited to gametes. (Zhao et al., 2012). Further experimentation will be needed to confirm this hypothesis.

RBR controls asymmetric cell division

Due to the presence of the cell wall, plant cells are not mobile and the plane of cell division that occurred during cytokinesis in the proliferative area will determine the mature tissue organization and the whole plant architecture. Early events in the formation of a new cell lineage imply the occurrence of an asymmetric cell division (ACD), also known as formative division, of a stem cell initial or of a cell with stem cell potential. This is, for example, the case of the establishment of the stomatal lineage, the initiation of lateral roots, or the formation of the ground tissue in the root. Several genes implicated in the specification of asymmetric division during embryogenesis (Ueda and Laux, 2012) or in the formation of different organs or tissues have been identified (De Smet and Beeckman, 2011). However, only recently a direct implication of the cell-cycle machinery has been established for the formative division at the root ground tissue (Sozzani et al., 2010; Cruz-Ramirez et al., 2012; Weimer et al., 2012).

The cortex and endodermis lineages are generated after two successive asymmetric divisions: the cortex/endodermis stem cell (CE1) divides anticlinally to self-renew and form a cortex/endodermis daughter cell (CEID) that, in turn, divides periclinally to initiate the cortex and endodermis layers. The
GRAS family of transcription factors SHORTROOT (SHR) and SCARECROW (SCR) are key players for the specification of these tissues and for the maintenance of the stem cell niche in the root meristem (Bennett and Scheres, 2010). It was reported that RBR interacts genetically with SCR to maintain the stem cell pool in the root meristem (Wildwater et al., 2005). It has been also shown that SCR also physically interacts with RBR through a canonical LxCxE motif and a combination of experimental and modelling studies demonstrated that the ternary complex formed by SCR–SHR–RBR modulates the expression of SHR–SCR targets and inhibits ACD in the endodermis outside CEID (Cruz-Ramirez et al., 2012). Several regulatory loops give robustness to the system and assure the spatiotemporal specificity of the ACD (Fig. 4). The radial movement of SHR from the stele to the endodermis where it is sequestered by SCR defines the layer (Cui et al., 2007). CYCLIN D6;1 (CYC D6;1) is a direct target of SCR/SHR, and its expression restricted to the CEID (Sozzani et al., 2010) depends on the interaction of RBR with SCR and also on an apical–basal auxin gradient along the endodermis layer (Cruz-Ramirez et al., 2012). Furthermore, phosphorylation of RBR by CDK/CYCD6;1 in the CEID releases RBR from the SCR–SHR–RBR complex triggering ACD. Even though CBKB1 binds and phosphorylates RBR in complex with CYCD6;1 in vitro, it seems that also CDKA;1 could supply this function. Thus, a null mutant of CKD;1 is severely compromised for cell-cycle progression and is not viable, but reduction of CDKA;1 activity in a series of cdka;1 hypomorphic mutants displayed a delay in the ACD of CEID, indicating that a high CDKA;1 activity is required for ACD (Weimer et al., 2012). Additionally, CDKB;1/CYCD6;1 complexes are able to phosphorylate in vitro the RBR pocket domain (Cruz-Ramirez et al., 2012) but the CEI/CEID phenotype of cdkb1;1 cdkb1;2 double mutant is much milder than that of the cdka;1 mutant, strongly suggesting a predominant role of CDKA;1 in ACD. Furthermore, the delay in ACD shown in the cdka;1 hypomorphic mutant can be partially suppressed when introgressed in a rbr mutant background, demonstrating that RBR is effectively the target of CDKA;1 (Weimer et al., 2012). However, expression of CDKB1;1 in a cdka;1 null mutant can partially rescue the CEID division, indicating that it must somehow participate in the pathway (Weimer et al., 2012). One possible explanation to the participation of both CDKA and CDKB1 is that they phosphorylate RBR sequentially, similarly to mammalian cells where different cyclin/CDK complexes participate in Rb inactivation (Munro et al., 2012). Finally, the last level of regulation of ACD is post translational. SHR, SCR, CYCD6;1, and RBR are degraded during or just before mitosis (SCR and RBR by the 26S-proteasome), resetting the system in the daughter cells and confining the ACD at the position of the CEID (Cruz-Ramirez et al., 2012). The interplay of CDKA;1 and RBR is also needed for the ACD that will initiate the stomatal lineage, targeting the stoma-specific transcription factor SPEECHLESS (Weimer et al., 2012). The role of RBR in these two cell-lineage formative divisions suggests that RBR could be a general regulator of formative divisions and lineage commitment along with specific transcription factors. Further research will be needed to challenge this hypothesis but it will be in line with recent findings in mammalian cells where RB together with differentiation-specific transcription factors was shown to influence cell fate choice in vivo (Calo et al., 2010).

**Perspectives**

The continuous organogenesis programme of plant development relies in a strict coordination between proliferative potential, cell-cycle exit to differentiation, and endoreplication. A complex gene network is being deciphered that regulates these pathways and among them RBR is positioned at a crossroad. In addition to its best-characterized function as a regulator of the G1-S transition and the endoreplication onset, RBR is emerging as a master regulator of many cellular processes, as it is discussed here and in the accompanying review article in this issue. Part of this multifunctional behaviour is mediated by the large amount of RBR.

**Fig. 4.** RBR in asymmetric cell division (ACD), showing the role of the RBR–SCR–SHR complex in regulating ACD for the formation of the root meristem ground tissue and the importance of RBR phosphorylation in disrupting the ternary complex. CEID, cortex/endodermis daughter cell.
interactors. It seems that RBR acts as a platform to recruit and/or deliver cellular factors to certain genome locations, including transcription factors, signalling components, and chromatin remodelling enzymes, among others. These interactions depend primarily on two RBR features: one is the modular organization of the protein and another the conformational changes that take place as a consequence of RBR phosphorylation. Most information on these structural–functional relationships comes from studies on animal Rb protein. However, the amino acid and module conservation between animal and plant Rb proteins supports that some functional activities that depend on certain structural changes are also conserved. In any case, the conservation of potential phosphorylation sites is not complete and therefore detailed studies on the role of specific phosphorylation sites on different RBR functions are needed. This is important not only for the cell-cycle E2F-dependent events but also for those involving the interaction with other cellular factors—e.g. chromatin, cell fate, cell division—for which no obvious counterparts with animal Rb can be easily identified. Therefore, we envision a whole set of genomic and proteomic analysis in the future that would shed light on the less-well defined functions of plant RBR during plant growth and development.

Acknowledgements

This work is supported by MINECO (grant BFU2012-34821 to CG and grant BFU2011-23434 to IRT) and by an institutional grant of Fundación Ramón Areces to the Centro de Biología Molecular Severo Ochoa.

References


DeCaprio JA. 2009. How the Rb tumor suppressor structure and function was revealed by the study of adenovirus and SV40. Virology 384, 274–284.


Goodrich DW. 2006. The retinoblastoma tumor-suppressor gene, the exception that proves the rule. Oncogene 25, 5233–5243.


