

DREAMs make plant cells to cycle or to become quiescent

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Highlights

- Activator and repressor MYB3Rs coordinately regulate the oscillation of mitotic genes
- E2Fs are not required for driving cell proliferation, but together with RBR for the exit
- RBR-E2FA inhibit differentiation to maintain proliferation competence
- Repressor MYB3Rs inhibit mitotic genes in differentiated cells
- RBR-E2Fs-MYB3Rs perform these functions as part of divergent DREAM-like complexes

Abstract

Cell cycle phase specific oscillation of gene transcription has long been recognized as an underlying principle for ordered processes during cell proliferation. The G1/S- and G2/M-specific cohorts of genes in plants are regulated by the E2F and the MYB3R transcription factors. Mutant analysis suggests that activator E2F functions might not be fully required for cell cycle entry. In contrast, the two activator-type MYB3Rs are part of positive feedback loops to drive the burst of mitotic gene expression, which is necessary at least to accomplish cytokinesis. Repressor MYB3Rs act outside the mitotic time window during cell cycle progression, and are important for the shutdown of mitotic genes to impose quiescence in mature organs. The two distinct classes of E2Fs and MYB3Rs together with the RETINOBLASTOMA RELATED are part of multiprotein complexes that may be evolutionary related to what is known as DREAM complex in animals. In plants, there are multiple such complexes with distinct compositions and functions that may be involved in the coordinated cell cycle and developmental regulation of E2F targets and mitotic genes.

Introduction

Plant growth and development are reliant on maintaining cell proliferation within meristematic zones, regulated by the perpetual transitions through cell cycle phases and the decision to enter into quiescence accompanied by cellular differentiation programs. The sequence of events through the cell cycle is underpinned by the oscillatory transcription of phase-specific genes, such as the cohort of early, G1/S-specific cell cycle genes, required for the entry into and progression through DNA synthesis, and late, G2/M-specific cell cycle genes with mitotic functions [1]. Gene expression profiling during synchronized cell cycle demonstrated that a significant proportion of genes, around thousand, are cell cycle regulated in yeast [2], human [3] and plant cells [4,5]. How these waves of transcription are connected is best understood in yeast, where the transcription factors themselves are periodically transcribed during the cell cycle and function to activate oncoming and inhibit previous regulators in a fully connected regulatory circuit [6]. However, the identity of the transcription factors and their regulation in metazoans and plants are distinct from that in yeast [7,8]. In animal and plant cells, the expression of early cell cycle genes are thought to be induced by the activator-type E2F family transcription factors [8,9], but it is becoming apparent that these E2Fs are not required to drive cell proliferation [9,10]. In plants, the late cell cycle genes are regulated by R1R2R3-Myb (MYB3R) family transcription factors [11]. When cells exit cell proliferation, both the G1/S and G2/M cohorts of cell cycle genes must be repressed to allow differentiation programs to commence. The timing of this program is a key determinant of organ size [12]. A fundamental question is whether the developmental down-regulation of cell cycle genes is due to active repression, as cells become quiescent, or the consequence of the lack of transcriptional activation. Recent studies provided clear evidence that the active repression of late cell cycle genes is mediated by the repressor-type MYB3Rs in differentiated cells and when this is abrogated, there is hyperplasia and larger organs; including seeds, roots and leaves [13]. The evolutionary conserved Retinoblastoma (Rb) protein, called RETINOBLASTOMA RELATED (RBR) in plants is another repressor that when silenced, the quiescence of plant cells is broken and cells over-proliferate [14,15].

Within the animal kingdom, the E2F, Myb and Rb are found to be part of a conserved protein complex, called DP, Rb-like, E2F, and MuvB (DREAM) in human, Drosophila RBF, E2f2 and Mip complex (dREAM) in fruit fly and DP, RB and MuvB complex

(DRM) in nematode [16-19] (for further details on DREAM complexes in different organisms; see Box 1). DREAM complexes have important roles in repressing cell cycle genes during quiescence and in the co-ordination of their phase-specific expression [17]. A recent work in *Arabidopsis* showed the participation of MYB3Rs, E2Fs and RBR in a common complex, suggesting that DREAM complexes are evolutionarily conserved between kingdoms [13,20]. Although the regulation of cell cycle genes by MYB3Rs and E2Fs have been studied and argued separately [8], the discovery of the large protein complexes containing both transcription factors give rise to the possibility of coordinated regulation of the early and late cell cycle genes during and as cells exit the cell cycle [21].

Activator E2F transcription factors might not be essential for cell cycle entry

The E2F transcription factors are considered to be the main regulators of early cell cycle gene transcription, but it is becoming apparent that they have much broader targets, including mitotic and cell cycle independent functions [9]. E2Fs were classified as repressors that in association with RBR impose quiescence and activators that when released upon RBR phosphorylation drives the entry into proliferation by transcriptional activation of cell cycle genes [22]. *Arabidopsis* holds three different E2Fs, nominated E2FA, E2FB and E2FC. E2FC is considered to be a repressor, because its overexpression down-regulated the replication initiation gene, *CDC6*, while its silencing increased *CDC6* expression and led to ectopic cell proliferation [23,24]. E2FC silencing effects are reminiscent to RBR co-suppression phenotypes, supporting the notion that these two proteins act together in a repressor complex [25]. E2FA expression peaks during S-phase and when overexpressed it induced the expression of S-phase genes [26]. This would indicate that E2FA is an activator, but studies with the overexpression of a C-terminally truncated mutant E2FA form that lost the abilities both for transactivation and for binding to RBR, yet it is fully capable to drive the expression of S-phase genes and to induce endoreduplication question this [27]. These experiments rather suggest that the release of E2FA from RBR repression is required for these functions. E2FB is uniformly expressed throughout the cell cycle, and when overexpressed it activates the expression of cell cycle genes, including the mitotic *CDKB1;1* and it leads to sustained cell proliferation even in the absence of auxin in cultured tobacco cells, suggesting an activator function [28]. However, mutants in E2F genes individually, or in combinations, such as the *e2fa/b* double [29] or *e2fa/b/c* triple [10] mutants are viable and only compromised in cell cycle

unrelated functions, such as resistance to pathogens [10]. Thus, in accordance to fly and mouse studies [22,30], activator E2Fs are not universally required for cell proliferation. It is becoming apparent that E2Fs in association with RBR are important as repressors to maintain meristem functions, ensuring cell survival and imposing quiescence during cell cycle exit. RBR and E2Fs also have cell cycle independent functions.

MYB3Rs shape the wave of G2/M-specific transcription

In *Arabidopsis*, approximately 180 late cell cycle genes are coordinately expressed during late G2 and M phases [31]. The transcription of this cohort of mitotic genes is regulated by the *cis*-acting MITOSIS-SPECIFIC ACTIVATOR (MSA) element in their promoters, where MYB3R transcription factors bind [11,32,33]. The *Arabidopsis* genome contains five genes encoding MYB3R proteins. MYB3R1 and MYB3R4 are closely related, the former is constitutive, while the latter is mitotically expressed [34]. The combined mutations in these two genes diminished the expression of the late cell cycle genes, suggesting that these two MYB3Rs are redundantly required for their transcriptional activation [31,34]. Consistent with the regulation of mitotic functions is the frequent occurrence of incomplete cytokinesis in the *myb3r1/4* double mutant that is largely due to the reduced expression of one of the targets, *KNOLLE*, involved in cell plate formation [34]. In tobacco cell culture, the mitotic MYB3R was shown to be activated through direct phosphorylation by CDKA in association with a mitotic cyclin [35, 36]. Mitotic cyclins are themselves transcriptionally activated by the activator MYB3R [35], thus constituting a positive feedback loop. The mitotically expressed MYB3R is also autoregulated through the MSA motifs in its own promoter [36]. These two amplifying mechanisms for the accumulation of activator MYB3Rs in turn triggers the burst of expression of downstream targets required for the entry and progression through mitosis (Figure 1).

In contrast to *MYB3R1* and *MYB3R4*, the other pair of highly similar *MYB3R3* and *MYB3R5*, when mutated together, led to the upregulation of mitotic genes both in proliferating and in non-proliferating quiescent cells, suggesting repressive functions [13]. During the cell cycle progression, these repressive MYB3Rs may operate as a mask to reduce the basal expression of mitotic genes outside their normal time window and thus to reinforce the periodic expression of these genes [13] (Figure 1). Surprisingly, MYB3R1 can synergize with MYB3R4 as an activator, while together with MYB3R3 and MYB3R5 it acts as a repressor [13]. This may suggest that MYB3R1 is part of the switch that

determines repressor activity outside the G2/M phase while at the G2/M transition, when CDK activity rises, MYB3R1 may become activated for transactivation by CDK phosphorylation, leading to the early induction of mitotic genes (Figure 1). This initial switch acting on MYB3R1 might get further amplified by the mitotically expressed MYB3R4 to trigger the full G2/M transition through the burst of late cell cycle gene expression.

Cell proliferation and differentiation, mutual exclusion?

Cell cycle genes are normally repressed in mature organs. For mitotic genes, this developmental repression is dependent on the repressor MYB3Rs [13]. This was demonstrated by the widespread occurrence of the *CYCB1;2* reporter in *myb3r1/3/5* triple mutant even in terminally differentiated cells, such as trichomes and root hair cells [13]. This suggests that in plants an active repression of mitotic transcription operates not only in developmentally quiescent, but even in fully differentiated cells. Upregulation of *CYCB1;1* was also observed when the E2FC transcription factor is silenced [24], but this needs to be confirmed in stable knockout mutant lines. Silencing of RBR delays [25], while overexpression instigate differentiation programs [37], suggesting that RBR is a key determinant for this transition. Therefore, RBR, E2Fs and MYB3Rs have similar roles in cell cycle exit and shared functions in the repression of cell cycle genes as cells differentiate. This is consistent with the finding that they are part of multiple repressor complexes (see below).

RBR also forms a repressor complex with E2FA, but this happens in proliferating cells within the meristem [37]. The RBR-E2FA complex is not disrupted by elevated *CYCD3;1* levels leading to increased RBR phosphorylation. It was suggested that the function of this RBR-E2FA complex is to repress differentiation genes, such as expansins and the endoreduplication-inducing *CCS52A* for the maintenance of cell proliferation in the meristems [37]. Whether the RBR-E2FA is part of a repressor complex is not yet known.

DREAM complexes with conserved and species-specific attributes

Using chromatin immunoprecipitation genome wide (ChIP-seq), it was shown that the repressor MYB3R3 not only associates with promoters of mitotic genes, but also with the early cell cycle genes that were previously defined as E2F targets [13]. Because these

early cell cycle genes show significant enrichment for E2F motifs, but not for MSA elements in their promoter regions, the DNA binding is not through MYB3R3. In agreement, co-immunoprecipitation experiments showed the association of MYB3R3 with E2FC and RBR [13], that evoked the existence of larger protein complexes known to bring together these two classes of transcription factors and Rb for the repression of cell cycle genes, called dREAM in fly [38]. Similar protein complexes were found in human and nematode, suggesting evolutionary conserved assemblies and functions [16] (Table 1, Box1). Searches for *Arabidopsis* genes orthologous to the core components identified ALWAYS EARLY (ALY) genes (orthologous to LIN9/Mip130), genes coding for the Tesmin/TSO1-like CXC domain-containing (TCX) proteins (orthologous to LIN54/Mip120) and the MULTICOPY SUPPRESSOR OF IRA1 (MSI1) [13] (Table 1). MSI1 is a histone binding protein that was shown to co-purify with HISTONE DEACETYLASE19 (HDA19)[39], and MSI1 together with RBR were found to be required for epigenetic regulation of imprinted genes [40]. However, there are no plant orthologues for the other core components, LIN37/Mip40 and LIN52 (Table 1). Thus, there is a convergence on some common DREAM complexes components in evolutionary divergent species, but there are important differences how these complexes assemble and function. In human cells, the common core complex (called MuvB core) either associates with E2F4/5 to impose G1 arrest or with the B-Myb or the mitotic forkhead class transcription factors, FoxM1 that function to induce the waves of S- and G2/M-specific gene expression [41]. In *Arabidopsis*, it appears that both the activator- and repressor-type DREAM-like complexes contain RBR, but in meristematic cells, E2FB and the mitosis-specific MYB3R4 is recruited to activate late cell cycle genes, while in mature leaves the repressor MYB3R3 and E2FC are present (Table 1, Figure 2).

The *Arabidopsis* DREAMs of cell cycle control

The existence of repressor- and activator-types of Myb-related transcription factors and their co-recruitment with the repressor E2FC or activator E2FB to RBR-containing DREAM-like complexes is a plant-specific utilization of these transcriptional regulatory module. How these divergent RBR containing DREAM-like complexes attain activator or repressor functions, how their dynamic interchange is regulated are largely unresolved questions. CDKA;1 was found to be developmental-specifically recruited to both MYB3R4 and MYB3R3 containing DREAM-like complexes [13]. RBR is an ancient

signal-dependent scaffold for protein interactions, regulated by multisite phosphorylations governed by CDKs. These phosphorylation events not necessarily leading to the disassembly of the complex, as was found in *Chlamydomonas* [42]. In animal cells, it was shown that Rb phosphorylation at distinct sites can diversify RBR complexes towards different functions, e.g. to become activator on certain batteries of genes while repressor on others [43]. Such diversification of RBR functions upon phosphorylation may also exist in plants, as suggested by the distinct association of E2FA and E2FB to RBR upon phosphorylation by CYCD3;1 dependent CDK, induced by sucrose [27]. RBR can also be targeted by phosphorylation through other signalling pathways, such as the stress-induced mitogen activated protein kinase [44], MPK6 that when mutated leads to hyperplasia, larger seeds, roots [45]. The phosphorylation status of RBR, a common component of multiple DREAM-like complexes in *Arabidopsis*, might determine the biochemical properties of the complex as well as its assembly and disruption.

Concluding remarks

Plant-specific properties of the multiprotein complex containing both E2F and MYB3R may provide new insights for various unsolved phenomena unique to plants. In plants, even the fully differentiated somatic and generative cells can be readily reprogrammed to become undifferentiated and capable of proliferating to allow organ regeneration or somatic embryogenesis [47]. A central part of this regeneration program is the de-repression of cell cycle genes, which may be mediated by the DREAM-like complex in plants. Plants may employ the mechanisms different from animals for establishing and maintaining the repressed state for cell cycle genes, which are more readily de-repressible upon stimuli. Future study should be focused on the molecular basis of post-mitotic repression mediated by DREAM-like complexes that may explain the extraordinarily high plasticity of plant cells.

Endoreduplication is integral to a number of plant developmental programs, which relies on the induction of early but repression of late cell cycle genes. This coordinated regulation of the cell cycle genes may require protein complexes where MYB3R and E2F may functionally interact with each other. It is known that E2F2 acts in opposition to Myb to repress some of the late cell cycle genes in fly dREAM complex [48]. Endoreduplication is also known to occur during pathogen infections in plants [46], for

instance it was reported that the mitotic MYB3R4 has an essential involvement in the induction of endoreduplication at the infection sites of the obligate biotrophic fungus, powdery mildew [47] suggesting that a DREAM-like complex may be integral for this cellular response caused by pathogens. Thus, there are accumulating evidence to suggest broader involvements of cell cycle regulators in plant responses to pathogens as well as to environmental factors [48][49]. The RBR-MYB3R-E2F complexes may provide convergence points to signaling mechanisms in biotic interaction, abiotic stresses, and development to coordinately regulate the expression of early and late cell cycle genes, thereby modulating cell proliferation, endoreduplication, or quiescence. Future research will have to address how these divergent DREAM complexes become hubs to regulate plant growth and development in tune with environmental conditions.

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References and recommended reading

Figure legends

Figure 1.

Schematic model for transcriptional regulation of the late cell cycle genes by activator- and repressor-type MYB3Rs in *Arabidopsis*.

In proliferating cells, the repressor-type MYB3Rs are responsible for keeping the late cell cycle genes suppressed outside of G2/M interval, until the transcriptional repression is lost concomitant with the activation of activator type-MYB3Rs. This switch-like transition triggers amplification of activator-type MYB3Rs through positive feedback loop mechanisms at transcriptional and post-transcriptional levels to enable the burst of target gene expression and irreversible entry into mitosis. In differentiated cells, the late cell cycle genes are stably maintained in a long-term silenced state by the function of repressor-type MYB3Rs.

Figure 2.

Regulation of cell cycle and quiescence by DREAM-like complexes in plants

In proliferating cells, the early cell cycle genes are repressed by the E2FB-DPA/B-RBR complex during G1. Phosphorylation of RBR by CYCD-CDKA;1 induces the release of active E2F-DPA/B to induce the transcription of early cell cycle genes. Later, E2FC may have a role in repressing transcription of the early cell cycle genes. This repression may be also accompanied by the action of DEL transcription factors, known as atypical E2Fs, which act as monomer in an RBR and DP-independent manner [50]. During G1, S and early G2, the late cell cycle genes are transcriptionally suppressed by the protein complex containing repressor-type MYB3R, RBR and possibly MuvB-like core complex. During late G2, this repressive complex on the target promoters is replaced by the MYB3R-E2F activator complex (containing activator-type MYB3R, E2FB, RBR, and MuvB-like core complex), triggering its auto-activation through the positive feedback loops and allowing transcription of the late cell cycle genes. In post-mitotic cells, the late cell cycle genes are kept in silenced state by the separate MYB3R-E2F complex with a repressive function (containing repressor-type MYB3R, E2FC, RBR and MuvB-like complex).

Box 1. DREAM complex

The DREAM (DP, Rb-like, E2F, and MuvB) complex is known as a key regulator to

achieve and maintain cellular quiescence by repressing cell cycle-regulated genes (both early and late cell cycle genes) in mammalian cells [51]. The DREAM consists of an Rb-related tumor suppressor family protein (p130 or p107), E2F family protein (E2F4 or E2F5) and its dimerizing partner DP, and a five-component MuvB core complex (LIN9, LIN37, LIN52, LIN54, and RBBP4). Interestingly, these DREAM components overlap with genetically-defined synthetic multivulval class B (MuvB) proteins in nematode [38], and shared with the evolutionarily conserved complexes that are biochemically identified from fly (dREAM) [17,38] and nematode (DRM) [52]. It should be noted that some of these complexes have synonyms when they were identified independently by the different groups, such as LINC (LIN complex) in human [53] and MMB (Myb-MuvB) in fruit fly [51], which are equivalent to DREAM and dREAM, respectively. The biochemical functions of these proteins are not known, with the exception of RBAP4 and LIN54, which have the abilities to bind histones and DNA, respectively. The mechanism of DREAM-mediated transcriptional regulation has not been well understood, but it is clear that its core complex recruits key cell cycle transcription factors, including E2F4/5, B-Myb, and FoxM1. In some cases, the complex are co-purified with chromatin regulators such as histone deacetylases and L(3)mbt that binds modified histones for chromatin compaction [54], suggesting transcriptional regulation through chromatin status.

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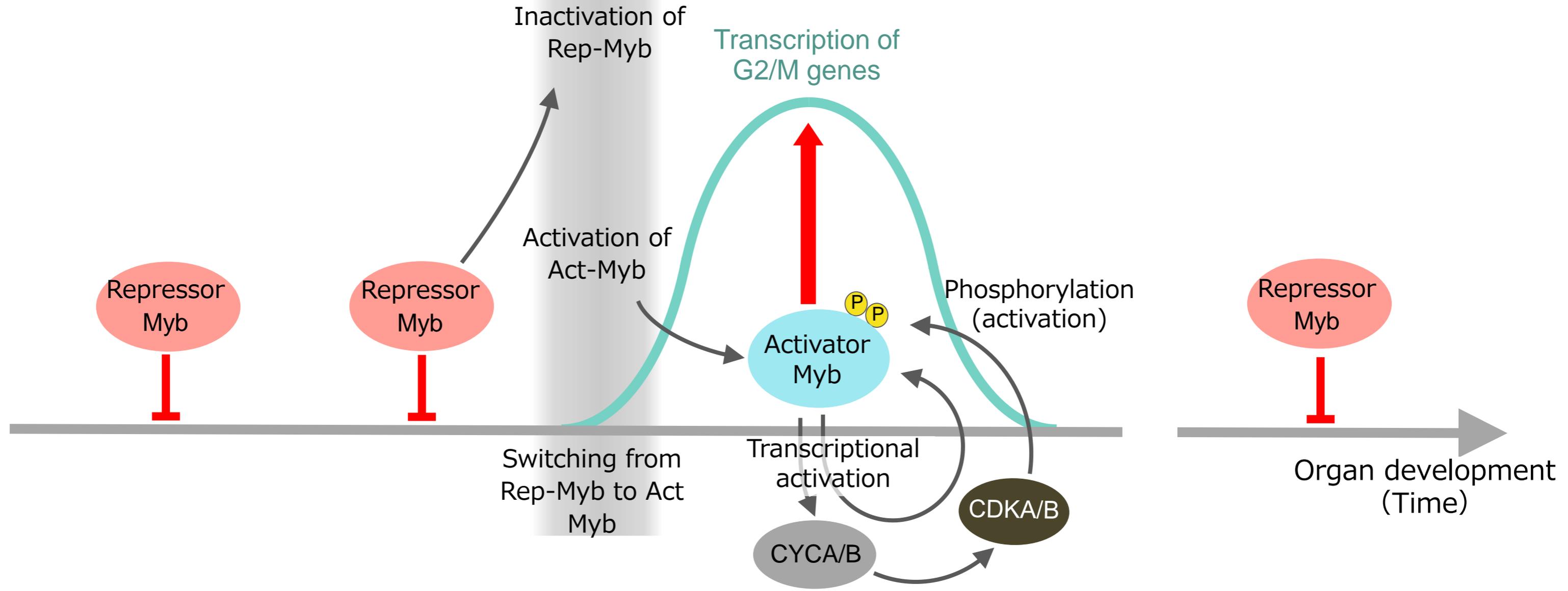
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Proliferating cells
(meristem, developing organs)

Differentiated cells
(fully developed organs)



Components of DREAM or related complex

Human (DREAM)	Fruit fly (dREAM/MMB)	<i>Arabidopsis</i> (DREAM-like?)		Function
		Activation?	Repression?	
B-Myb	dMyb	MYB3R4	MYB3R3	Sequence-specific DNA binding
E2F4/5	E2F2	E2FB	E2FC	Forming dimer with DP to bind DNA
DP1/2/3	Dp	DPA	?	Forming dimer with E2F to bind DNA
p107, p130	Rbf1, Rbf2	RBR	RBR	Binding to E2F to inhibit transcription
LIN9	Mip130	ALY3	ALY2, ALY3	Binding to DNA with A/T-rich sequence
LIN54	Mip120	TCX5	TCX5	Sequence-specific DNA binding
RBBP4	Caf1 (p55)		MSI1?	Binding to chromatin
LIN37	Mip40	No homolog in plants		Unknown
LIN52	dLIN52	No homolog in plants		Interacting with p107/p130
FoxM1	?	No homolog in plants		Sequence-specific DNA binding
	L(3)mbt	No homolog in plants		Binding to methylated histone
HDAC3	Rpd3		HDAs?	Histone deacetylase

