DREAM a little dREAM of DRM: Model organisms and conservation of DREAM-like complexes

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Received: 7 July 2023 | Revised: 23 November 2023 | Accepted: 24 November 2023

DOI: 10.1002/bies.202300125

BioEssays

REVIEW ESSAY

Prospects & Overviews

DREAM a little dREAM of DRM: Model organisms and conservation of DREAM-like complexes

Model organisms uncover the mechanisms of DREAM-mediated transcription regulation

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Funding information
Ligue Contre le Cancer

Abstract

DREAM complexes are transcriptional regulators that control the expression of hundreds to thousands of target genes involved in the cell cycle, quiescence, differentiation, and apoptosis. These complexes contain many subunits that can vary according to the considered target genes. Depending on their composition and the nature of the partners they recruit, DREAM complexes control gene expression through diverse mechanisms, including chromatin remodeling, transcription cofactor and factor recruitment at various genomic binding sites. This complexity is particularly high in mammals. Since the discovery of the first dREAM complex (drosophila Rb, E2F, and Myb) in *Drosophila melanogaster*, model organisms such as *Caenorhabditis elegans*, and plants allowed a deeper understanding of the processes regulated by DREAM-like complexes. Here, we review the conservation of these complexes. We discuss the contribution of model organisms to the study of DREAM-mediated transcriptional regulatory mechanisms and their relevance in characterizing novel activities of DREAM complexes.

KEYWORDS
DREAM complex, E2F family, MMB complex, transcription

INTRODUCTION

Cell division is essential in all living organisms since it allows their development and growth. Guardians of the cell cycle progression are needed to ensure proliferation does not get out of control. One of those guardians is pRb (Retinoblastoma protein), the first tumor suppressor identified,[1] which is a member of the conserved pocket-protein family named RB family. pRb is known to regulate cell proliferation and differentiation, notably via interaction with E2F family transcription factors, which activate S phase genes. This interaction can be found in pluricellular eukaryotes such as mammals, invertebrates, or plants.[2] In *Drosophila melanogaster*, pRb homologs are Rbf1 and Rbf2.[3] The search for new partners for Rbf1 led scientists to identify several co-purifying proteins forming a transcription regulator complex named dREAM or Myb-MuvB (MMB).[4–6] Homologs of DREAM/MMB subunits have been found from *Caenorhabditis elegans*[7] to human[8,9] and

Arabidopsis thaliana.[10] In all of these multicellular eukaryotes, they were found to associate into a DREAM-like complex organized around a core of three to five subunits depending on the species.

In this review, we report how genetic, molecular biology and biochemical approaches together with omic studies identified DREAM-like complexes as transcriptional activators or repressors of a broad spectrum of target genes. Regulation of target genes expression depends on the complex composition. The subunits present in the complex drive its binding to specific target sites and modulate transcription by recruiting different partners, such as transcription activators or chromatin remodelers. The variety of model organisms studied allowed the identification of a diversity of recruited partners. Altogether, this multiplicity of subunits, partners and targets underlines the difficulty of studying the activity of DREAM-like complexes. Interestingly, the complementarity of the approaches taken and the accumulation of data in the different model organisms revealed that DREAM-like complexes regulate major biological processes. While DREAM complexes are widely described as controlling the cell cycle in mammals, studies on other model organisms highlight that these complexes may regulate other essential cellular processes. The objective of this review is not to exhaustively describe all the data reported on these complexes but to focus on the contribution of model organisms concerning DREAM complexes composition, their transcription regulation mechanisms, and their role in cell fate.

DREAM: A CONSERVED COMPLEX

Initially, the transcription regulation complex dREAM has been discovered in *D. melanogaster*. It is notably constituted of RB/E2F family members. Since these major cell cycle regulators are found in numerous eukaryotes, this observation led scientists to investigate the conservation of this complex structure. One interesting finding is that DREAM-like complexes are found from mammals to plants with different compositions, even within the same organism, as described in *D.* melanogaster and mammals (Table 1).

The discovery of the dREAM complex in *Drosophila melanogaster*

In mammals, the RB family has been extensively studied for its role in cell cycle progression by interacting with the E2F/DP (Dimerization Partner) heterodimer. Besides its RB family members Rbf1 and Rbf2, the *D.* melanogaster genome encodes dDP, a unique DP family member, and dE2F1 and 2, two E2F family proteins. In this invertebrate, Rbf1 and dE2F1-2/dDP also control transcription of cell cycle gene regulators.

In 2004, purification of this *D. melanogaster* Rbf1-2/dE2F2/dDP complex by chromatography revealed the presence of several copurifying proteins: Mip120 (Myb-interacting protein of 120 kDa), Mip130, Rbf1, Rbf2, dDP, dE2F2, Caf1p55, Mip40 and the transcription factor dMyb in nuclear embryo extracts.[4] This newly found complex was called drosophila Rb, E2F, and Myb (dREAM). Interestingly, a few years earlier, Myb had already been found in a complex containing Mip130, Caf1p55, and Mip40.[6] Another study focusing on Myb purified a complex containing all dREAM subunits and dLin52.[5] This complex was named Myb-MuvB (MMB) since all its subunits are encoded by homologs of the *C. elegans synMuvB* genes with the exception of Myb.

DRM in *C.* elegans

The discovery of the *D. melanogaster* dREAM complex composed of the so-called SynMuvB genes-encoded homologs led to focus on these genes. They are involved in Ras-mediated signaling which induces vulva development. Mutations in those pathways are responsible for vulvaless (vul) phenotypes when downregulated and ectopic vulva (multivulva, Muv) phenotypes when upregulated. Studies of these phenomena led to the discovery of the synthetic multivulva (SynMuv) gene class, initially divided into class A and class B genes, depending on the mutation they carried.[11] Gel filtration and co-immunoprecipitation experiments on SynMuvB gene products led to the discovery of the *C. elegans* dREAM counterpart, the DRM complex[7] (Table 1).

DNA targeting of the DRM complex is mediated by EFL-1/DPL-1 and the DNA-binding domains of LIN-54.[12] The RB family protein LIN-35 acts as a scaffold to mediate the association between MuvB and EFL-1/DPL-1, but its absence does not entirely abolish their association with DNA at few promoters targeted by DRM. Loss of LIN-35 induces the up-regulation of numerous DRM target genes. However, it remains to be tested whether LIN-35 is essential for repression or whether this upregulation is an indirect effect due to reduced occupancy by other subunits.[13]

Unlike in *D. melanogaster*, no Myb-MuvB complex has been observed in *C. elegans*, as no Myb homolog has been identified in *C. elegans*. However, expression of a *D. melanogaster* Myb in *C. elegans* causes a SynMuv phenotype[14] and LIN-9 and LIN-52 proteins conserve their Myb-binding domains, suggesting that a Myb homolog, once present in a common ancestor, was lost in the *C. elegans* branch.[14,15] Given the results observed in *C. elegans*, it is now accepted that *D. melanogaster* possesses a MuvB core, which can associate either with Rbf1-2, dE2F2 and dDP, or with Myb, or all four proteins (Table 1).

DREAM in mammals

After the discovery of *D. melanogaster* and *C. elegans* dREAM/DRM complexes, the existence of homologs for most of the subunits described in these organisms led researchers to wonder if such a complex existed in mammals. This is indeed the case, but a higher level of complexity occurs in mammals due to a higher number of homologous proteins. For example, the RB family, which includes three proteins in mammals, that is, pRb, p107, and p130, is represented by only two proteins in *D. melanogaster* (Rbf1-2) and the sole *C. elegans* LIN-35 protein.

TABLE 1 Table of dREAM members homologs.

Organism	*Drosophila melanogaster*	*Caenorhabditis elegans*	Mammals	*Arabidopsis thaliana*	Function			
Complex	dREAM/Myb-MuvB + tMAC	DRM	hDREAM/LINC/ DREAM/MMB	DREAM	Targeting	Binding	Recruitment	Assembly
Protein homologs	Rbf1/Rbf2	LIN-35	p130/p107	RBR1	○	● Ce Dm	● Ce	● Ce
	dE2F2*	efl-1*	E2F4-5*	E2FB (+) / E2FC (–)*	● Ce Dm Mm	● Ce Dm Mm	● Dm	● At
	dDP*	dpl-1*	DP1*	DPA/DPB*	*See previous line*			
	Myb*	–	B-MYB*	MYB3R3 (–) / MYB3R4 (+)*	● Dm Hs	○	● Hs	○
	Mip40	LIN-37	LIN37	–	○	● Hs	○	○
	Mip120*	LIN-54*	LIN54*	TCX5*	● Ce Dm Hs	● Ce Dm	● Dm	○
	Mip130	LIN-9	LIN9	ALY2/ALY3	○	● Dm	● Hs	● Hs
	Caf1p55	LIN-53	RBBP4	mSI1	○	○	● Dm Hs	○
	Lin52	LIN-52	LIN52	–	○	○	○	● Hs
	–	–	–	BTE1	○	○	○	○

Minus signs indicate an absence of homologs. (+) and (–) indicate members that are respectively activators or repressors of transcription. Names in blue indicate subunits of the complex core. Proteins possessing DNA-binding domains are tagged with an asterisk. The involvement of each subunit in targeting and binding genes, recruiting partners and assembling the complex are indicated in the right part of the table. A white dot indicates that either no data has been found on this matter or the subunit does not have this function. A black dot indicates that the subunit is involved in this function in the organism indicated below (At : Arabidopsis thaliana, Ce: *Caenorhabditis elegans*, Dm: *Drosophila melanogaster*, Hs: *Homo sapiens*, Mm: *Mus musculus*). For functions that are suggested but not yet proven, the name of the organism is written in grey. Since DP and its homologs are usually studied in the DP/E2F complex, data for these subunits is regrouped.

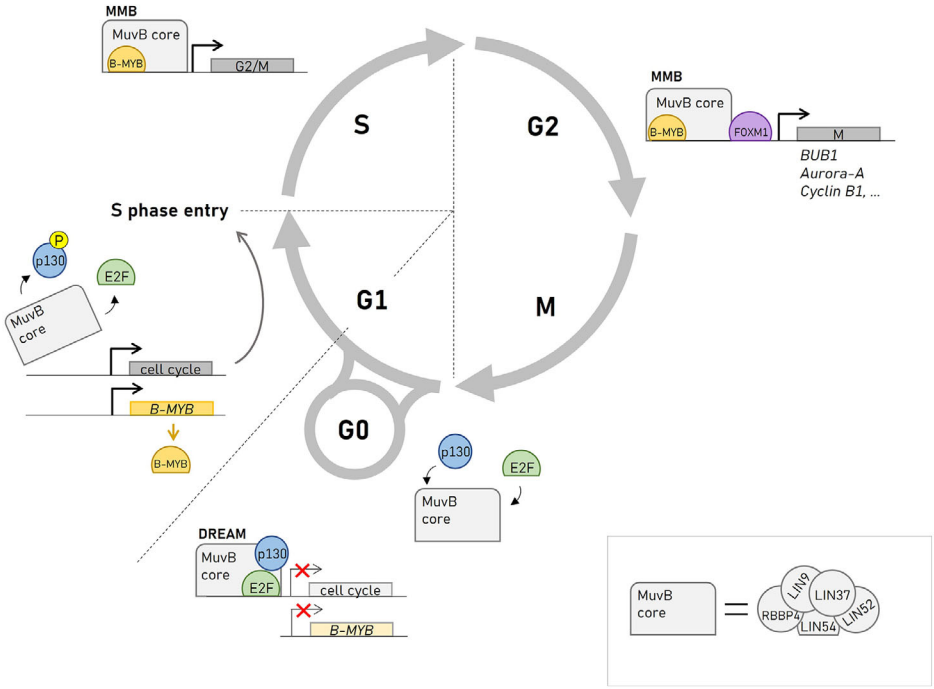

FIGURE 1 Regulation of the binding of B-Myb and p130/E2F4 to the MuvB core complex during the mammalian cell cycle. During the G1 phase, DREAM subunits are phosphorylated by cyclin-dependent kinases such as CDK2 and CDK4. Among these post-translational modifications, p130 phosphorylation leads to the disruption of the DREAM complex."[9,18] After p130/E2Fs dissociation, the MuvB core, whose subunits are indicated in the bottom right-hand corner of the figure, binds to DNA through an interaction of LIN54 with Cell cycle genes Homology Region (CHR) promoter elements,[23,24] leading to the entry in S phase. B-MYB is then produced and recruited to the MuvB core to form the MMB complex.[17] This complex does not bind E2F target genes anymore but activates genes implicated in the G2/M phase [25]. The MMB remains associated during the G2/M phase. It can then recruit additional transcription factors,[26] such as FOXM1.[26] The MMB complex activates key mitotic genes like Cyclin B1 for entry in the M phase, BUB1 for the mitotic spindle checkpoint, or Aurora A for the spindle assembly.[27] After cell division, LIN52 is phosphorylated on its serine 28 by DYRK1A, allowing the binding of p130 to the MuvB core and thus reassembly of a DREAM complex containing RB and E2F-DP family proteins. Overexpression of B-MYB or expression of LIN52-S28A disrupts DREAM assembly and promotes MMB formation.[28]

Immunoprecipitation experiments first showed that a complex was formed by the homologs of dREAM/DRM complexes.[8,9] Not all RB family members participate in the mammalian complex called DREAM or LIN complex (LINC), p130 being the main one involved.[8] p107 can also be found in the complex,[9] but its role remains unclear even if it might replace mutated p130 in the complex. Even if initial data obtained by gel filtration and co-immunoprecipitation with LIN9 found pRb associated with MuvB core subunits,[9,16] pRb was not found to co-immunoprecipitate with LIN54, or LIN37.[8,17] A major element pointing toward the absence of pRb in the DREAM complex is that no repression of the studied DREAM targets can be observed if p130 and p107 are inactive.[8] The inability of pRb to be incorporated in the DREAM complex results from structural differences between pRb and p130/p107 that impede pRb binding to LIN52.[18] Therefore, it is now accepted that only p130 and p107 can be part of the DREAM complex while pRb can cooperate with the DREAM complex to control G1/S transition but not G2/M checkpoint.[19,20]

In mammals, the DREAM complex specifically refers to a complex in which E2F and pRb family proteins are added to the MuvB core, whereas the complex named MMB (Myb-MuvB) is formed of the MuvB core added of one of the Myb family members.[21] Similarly to pRb family proteins, not all three MYBs (A-MYB, B-MYB, and C-MYB) are involved in the DREAM complex activity; only B-MYB co-immunoprecipitates with LIN9,[22] LIN37, and LIN54 but not with p130.[8] Mass spectrometry experiments also detected a minor A-MYB signal in MMB complexes in human cells.[8] The C-terminus region of B-MYB contains a Muv-binding domain (MBD) that allows the interaction with LIN9 and LIN52. This domain differs between each Myb, explaining the binding bias to the MuvB core.[15] Therefore, both mammalian DREAM and MMB differ from the *D. melanogaster* dREAM complex by their composition. Rbf1-2 and Myb can be found in the same complex in *D. melanogaster*, whereas in mammals only the DREAM complex contains the p130 RB family protein and the MMB complex includes B-MYB (Table 1). These two mammalian complexes seem tightly linked to the progression of the cell cycle with DREAM and MMB being associated with distinct cell cycle phases, as described in Figure 1.

DREAM-like in plants

In plants, homologs of dREAM members exist. In monocotyledons such as maize or rice, two main pRb subfamilies exist, with members

Box 1: Myb proteins in plants and the DREAM complex

There are hundreds of Myb domain-containing proteins in plants, but only a few are similar to mammalian and *D. melanogaster* Myb family proteins. Due to the triple repetition of their DNA-binding domain, this group of proteins is called R1R2R3-Myb or Myb3R. Some of them are transcription activators (Myb3R4), while others repress transcription (Myb3R3 and Myb3R5).[32] Myb3R1 was first believed to be a transactivator, but this effect seems to depend on the presence of Myb3R4. Conversely, MYB3R1 represses transcription in the presence of MYB3R3 or MYB3R5. It has been suggested that MYB3R1 might be a switch between transcriptional activator and repressor activities of the DREAM complex.[34] Consistently with their opposite roles, MYB3R3 and MYB3R4 are found in those DREAM-like complexes in a mutually exclusive manner. They are respectively associated with the transcription repressor E2FC and the transcription activator E2FB.[32,34] Therefore, plant DREAM-like complexes also seem able to activate or repress transcription depending on the recruited Myb3R protein.

involved either in the negative cell cycle regulation or endosperm development.[29] In the dicotyledon named *Arabidopsis thaliana*, Rb-Related 1 (RBR1) is the sole pocket protein and is closer to mammalian pRb than to other mammalian pocket proteins. As in animals, its association with E2F and DP family proteins mediates RBR1 action. *A. thaliana* contains two DPs (DPA and B) and six E2Fs, but only three of them (E2FA, B, and C) possess a dimerization domain as observed in E2F family proteins found in animal models and human.[30] Using pull-down and mass spectrometry experiments, the interaction study between RBR1, E2FB or C, DPA or B and homologs of the MuvB core proteins revealed the existence of DREAM-like repressor and activator complexes. No plant homolog was found for Mip40/LIN37 and LIN52.[31,32] However, a plant-specific subunit has been identified by co-immunoprecipitation of *A. thaliana* DREAM complex subunits and mass spectrometry: BTE1/DCR2.[10,33] These complexes also contain Myb homologs,[32] as described in Box 1. One last subunit found in DREAM-like complexes in plants is CDKA, which may regulate the complex assembly and composition through phosphorylation of DREAM subunits.[29,34] Therefore, plant DREAM-like complexes display a composition that is slightly different to their animal counterparts with only three of the five core subunits.

What about other model organisms?

In the zebrafish *Danio rerio* and in *Xenopus tropicalis*, orthologs for the core proteins Mip120/LIN54 and Mip130/LIN9, as well as for pRb family and Myb proteins can be found in online databases such as Flybase. Despite this, no study is published yet on the existence or the absence of dREAM-like complexes in *X. tropicalis*. On the opposite, Shepard et al. described a role of *D. rerio* B-MYB in the gene transactivation during G2/M phases [35] and Yamauchi et al. reported the interaction of Myb with the core dREAM protein Mip130/LIN9,[36] suggesting that a dREAM-like complex may exist in *D. rerio*.

Interestingly, no ortholog of Mip120/LIN54, Mip130/LIN9, or Rbf1 has been identified in *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*. Therefore, dREAM-like complexes do not seem to exist in yeasts. Overall, this suggests that a yeast ancestor has lost the DREAM complex subunits that probably existed in its common ancestor with plants and animals.

A TRANSCRIPTION REGULATION COMPLEX

Are DREAMs transcription activators or repressors?

The activity of DREAM complexes was discovered through the inactivation of some of its subunits by mutation or RNA interference (RNAi) in *D. melanogaster*,[4,37] *C. elegans*,[12] and mammalian cells.[8] When discovered in *D. melanogaster*, dREAM seemed to be mainly a transcriptional repressor complex. As a matter of fact, more than 600 of *D. melanogaster* genes were up-regulated when one or more of DREAM subunits were down-regulated by expressing specific RNAi. All members of the dREAM/MMB complex were targeted except Caf1/p55. On the opposite, almost as many genes were down-regulated in the same conditions, suggesting that dREAM/MMB can both activate and repress transcription.[38] Similarly, in *C. elegans* embryos and germline cells, mutants of LIN-54 led to the upregulation of more than 700 genes and the down-regulation of 550 others.[12] Finally, in mammalian cells, the expression of RNAi targeting LIN9 or LIN54 mRNAs suppressed transcriptional repression of DREAM-regulated genes. However, due to the higher number of homologous genes in mammals, it is harder to decipher the effect of downregulating DREAM complex regulators. For example, the loss of p130 can be compensated by a spontaneous increase in p107 transcription.[8,19] Altogether, data from invertebrate models and mammals strongly suggest that DREAM-like complexes have both activator and repressor activities on transcription.

To further characterize the target genes of DREAM-like complexes and more finely identify DREAM binding sites, different chromatin immunoprecipitation techniques have been used. ChIP-on-chip experiments using antibodies against almost all dREAM/MMB subunits allowed the identification of more than 3500 binding sites in *D. melanogaster* cells. However, only 25% of the genes with a peak near their promoter sequence show an expression change when dREAM subunits are down-regulated by RNA interference,[38] suggesting that the interaction of DREAM-like complexes with DNA is not sufficient to cause a change in the level of transcription.

Part of the target genes of DREAM-like complexes is conserved through evolution. LIN-54 binds to almost 2000 locations in the *C. elegans* genome, including 1572 protein-coding genes. Among the 3015 orthologous genes found to be shared by *D. melanogaster* and

C. elegans, around 1200 are bound by *D. melanogaster* Mip120, and 650 by its *C. elegans* homolog LIN-54. Cross-referencing these lists led to the identification of 327 genes that are bound by Mip120/LIN-54 in both invertebrates.[12] Among these numerous targets, DREAM complexes can bind the promotor region of some of the genes encoding DREAM subunits but do not seem to regulate their transcriptional activity.[8,12,38]

Overall, although dREAM was initially described as a repressor complex, RNA interference and chromatin immunoprecipitation (ChIP) studies showed that DREAM complexes can bind thousands of promoters to activate or repress their transcriptional activity, or more surprisingly, with no detected effect on target gene expression. Therefore, transcriptional DREAM complexes-mediated regulation appears complex. Their high number of targets combined with various possible effects on transcription makes it very difficult to predict DREAM complexes' activity at a given promoter and the high genetic redundancy observed in mammals highlights how crucial the use of animal models is when studying these complexes.

How do DREAMs regulate transcription?

Although ChIP experiments identify the promoters bound by DREAM complexes, they give little information on the mechanisms of regulation mediated by these complexes. Since none of the DREAM subunits seem to carry enzymatic activity, its components that do not possess a DNA-binding domain (i.e., Rbf1, Rbf2, Caf1p55, Mip40, Lin52) might play a role in stabilizing the complex or recruiting other partners such as chromatin-modeling enzymes. DREAM complexes regulate transcription through multiple processes, some of which require the recruitment of partners. The multiple facets of these regulations add yet another complexity to how these complexes work.

Influence of the complex composition

The first and most obvious way for DREAM to regulate transcription is through the activity of its subunits. Firstly, the composition of the complex determines its target genes and its binding sites. In *D. melanogaster*, DNA-binding subunits, such as Mip120 (the LIN-54 homologue) and dE2F2, have specific target sequences that allow the complex to bind a wide range of genes. dE2F2 and Myb seem to be the main driving force of DREAM binding.[38] In *C. elegans*, which encodes no Myb, ChIP-qPCR, experiments on *lin-54* mutant worms have shown that LIN-54 is involved in recruiting DRM at promoters. Moreover, LIN-54 binding is enriched at sequences that contain a binding motif for LIN-54 adjacent to an E2F-binding motif.[12] Consistently, DRM association with chromatin is done primarily through the DBD domains of E2F-DP and the tesmin domains of LIN-54.[12,13] However, subunits that contain a DNA-binding domain are not the only factors that regulate DREAM binding, since interaction with DNA is also impaired by the absence of LIN-35.[13] Therefore, DNA-binding subunits of DREAM-like complexes participate in the choice of target genes in both invertebrate models but are not the sole subunits involved in this preference.

Secondly, the complex composition controls target genes activation or repression. The subunits found in DREAMs sometimes differ at promoters. For example, the *how* gene promoter is bound by the MMB in *D. melanogaster* wing imaginal disc cells to activate transcription,[39] while in embryonic cells it is repressed by the dREAM complex.[38] Systematic RNA interference against the different subunits of dREAM in *D. melanogaster* cells helped determine the role of these proteins in gene targeting. Mip120 and Mip130 have been identified as necessary for the binding of all the tested target genes. Targeted genes were then classified into multiple categories depending on which dREAM/MMB subunits were essential for their regulation and whether they were activated or repressed.[38]

Since the identification of Myb as a dREAM complex component in *D. melanogaster*, this protein was considered a silent member of the complex when it represses transcription. This hypothesis was based on both the literature that mostly describes the transactivating role of Myb, and the Myb-knock-down-independent transcriptional repression of dREAM target genes.[5] However, since this first study, Georlette et al. classification brought to light the antagonistic effects of Rbf1-2/dE2F2 and Myb: Rbf1-2/dE2F2 are mainly present in repressive complexes, while activating complexes always contain Myb. Complexes including at the same time Rbf1-2 and Myb are repressive, suggesting a dominant effect of Rbf1-2 over Myb (Figure 2).[38,40]

This antagonistic effect can be observed in other species (Figure 2). As detailed in the third part of the review, depending on the cell cycle phase, mammalian RB/E2F and MYB family proteins can associate to the MuvB core in a mutually exclusive manner to respectively form the DREAM or MMB complexes.

DREAM binding sites as a clue on how DREAM affects transcription

dREAM mainly binds transcriptionally inactive regions, which supports the hypothesis of its repressive activity. Immunostaining of dREAM subunits on *D. melanogaster's* polytene chromosomes revealed a location on repressed chromatin and no colocalization with phosphorylated RNA polymerase II, a marker of actively transcribed regions. Consistently, Rbf1, Rbf2, and Mip130 subunits associate to non-acetylated histone H4 tails in peptide-binding assays, but not to acetylated H4, showing another repressed-chromatin-binding preference. Hypothesizing a role for this preference, Korenjak et al. proposed that dREAM complexes bind deacetylated histones to maintain them in a repressed state and protect them from further modification.[4]

Numerous genomic studies have been done to decipher the dREAM complex roles in transcription regulation, revealing that dREAM binds promoter-proximal locations in gene-dense regions of different organisms: 86% of dREAM-bound regions are within 1 kb of transcription start sites (TSS) in *D. melanogaster* cells[38] and 78% between −1000 and +100 bp from TSS in *C. elegans* embryos. In contrast, the 22% left in these embryos were located in inactive regions such as introns or

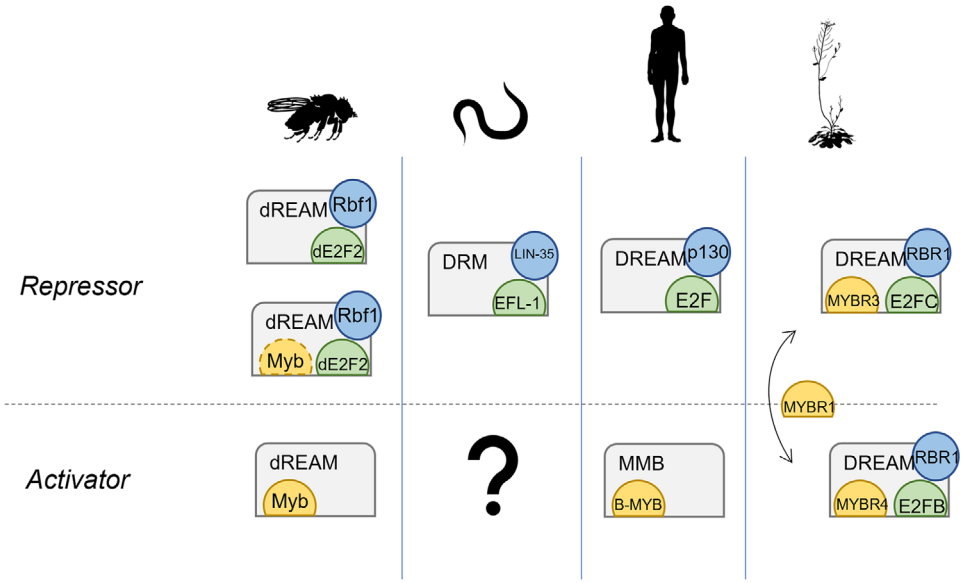

FIGURE 2 Antagonism of Rb-family and Myb-family members. Composition of transcription repressing and transcription activating complexes in (from left to right) *D. melanogaster*, *C. elegans*, *Homo sapiens*, and *A. thaliana*. In *D. melanogaster*, Myb can be observed in both dREAM and MMB complexes but it does not seem to affect the dREAM activity. In mammals, p107 can also be found in DREAM complex instead of p130. Gray boxes represent the core and/or other members of the complex. In *A. thaliana*, MYBR1 can be found either in E2FB- and E2FC-containing complexes and may play the role of a switch between transactivating and trans-repressive complexes (see Box 1).

intergenic regions.[13] Therefore, the transcriptional role of DREAMs seems to be carried out through promoter binding.

Interestingly, DREAM-like complexes seem to interact with nucleosomes. It has been shown that DREAM-bound genes display a nucleosome-depleted TSS region upstream of high nucleosome occupancy regions. Therefore, these promoters have an "expressed gene" nucleosome-free TSS profile but a "repressed gene" coding region profile with high nucleosome occupancy. This mechanism may allow to keep repressive nucleosomes in place until the timing of expression is right. [41] A recent study showed that the mammalian MuvB core associates with the closest nucleosomes located downstream of the TSS and that this association correlates with gene repression. MuvB may once again stabilize nucleosome position by forming a bridge between nucleosomes and DNA. This mechanism has been hypothesized to contribute to repression by inhibiting chromatin remodeling or the activity of transcription proteins such as polymerases.[42] This type of regulation may be conserved in *D. melanogaster*, as dREAM binding at TSS seems to play a part in regulating divergently paired genes (DPG) that are genes transcribed in the opposite direction with close TSS (less than 1000 bp), accounting for a third of fly genes.[43] In mammals and *D. melanogaster*, DREAM complexes thus seem to hold repressive nucleosomes in place to maintain expression repression. On the contrary, the MMB complex, which activates M-phase genes in mammals, binds to nucleosomes to free and expose DNA. This could allow the binding of the transcription machinery.[44] Binding to nucleosomes thus seems an important way for DREAM and MMB complexes to regulate transcription by maintaining unwinding of nucleosome-bound DNA.

DREAMs recruit other partners to modulate transcription

Although binding sites and composition of DREAM complexes are important factors in the regulation of transcription, DREAMs can also recruit partners to modulate gene expression. Those partners can act directly on promoters or at a higher level by modifying the chromatin state.

Transcription repressors and factors recruitment

Despite a variable composition that can go up to nine subunits, DREAMs also recruit or interact with other proteins to regulate transcription. One of these proteins, L(3)MBT (lethal (3) malignant brain tumor), is sometimes considered an accessory subunit. It was identified by a mass spectrometry approach destined to find Mip120 partners[5] and this interaction was confirmed by co-immunoprecipitation and GST-pulldown experiments.[38,40] This transcription repressor is capable of binding chromatin[45] and has been found to be associated with transcription regulators such as insulator-binding proteins[46] and H4K20 methylations in *D. melanogaster*.[47] Mip120 is critical for L(3)MBT correct localization on chromatin. On the opposite, Mip130 and dE2F2 are not necessary for this binding but mutated dREAM subunits mimic a loss of function of L(3)MBT at least for some of its targets, suggesting that these dREAM subunits are involved in L(3)MBT-mediated repression.[40] In mammals, even though no interaction has been shown between MuvB core proteins and L(3)MBTL1, the homolog of L(3)MBT, this protein nevertheless binds to E2F target sites.[48] These data thus suggest that L(3)MBTL1 may participate

in the recruitment of both *D. melanogaster* and mammalian DREAM on DNA.

Even if some of the DREAM subunits are transcription factors, they are not the only proteins that can intervene in the transcription regulation activities of the complex. Promoter-binding studies such as chromatin immunoprecipitation of DREAM subunits have revealed enrichment for transcription factor binding sequences in the regions bound by this complex. As expected, the most represented are the E2F- and CHR-binding sequences respectively during the G1/S and G2/M phases.[49] In mammalian cells, the prediction for enriched sequence motifs identified B-MYB, but also CREB and NRF2-binding sequences, suggesting that these transcription factors can cooperate or compete with the DREAM complex to regulate the transcription of their targets.[8] Likewise, Goetsch et al. compared in *C. elegans* the DRM peak regions they found by ChIP to high occupancy target (HOT) regions[13] that are genomic regions with many transcription factor binding sites. They observed that around a third of their high confidence DRM peaks correspond to HOT embryonic regions, suggesting interaction with other transcription factors, and revealing potential partners for DREAM complexes.

Additionally, the mammalian transcription activator FOXM1 has been identified in motif enrichment analysis of MuvB core binding sites,[26] and co-immunoprecipitation confirmed this interaction. This binding to MMB may depend on B-MYB[26,50] or LIN9[51] and is essential for the expression of some mitotic genes. Therefore, FOXM1 can be considered an accessory MMB subunit. This binding cannot be extrapolated to invertebrates since no homolog of FOXM1 has been identified in *D. melanogaster* and *C. elegans*.[25]

The co-activator of transcription of the Hippo pathway named YAP regulates genes involved at different steps of the cell cycle, including G1/S, mitosis, and cytokinesis. by binding enhancers.[52] YAP cooperation with the MMB complex was thus investigated in mammals, showing that YAP can interact with the Myb and LIN9 MMB subunits, probably through chromatin looping. Consistently, the MMB complex was found to be required for YAP-mediated expression of G2/M genes.[53] YAP may be particularly important in the MMB activity since Myb and FOXM1 appear to be among its targets,[53,54] but this has to be studied more thoroughly and model organisms could be useful in this study.

Altogether, these data suggest that DREAM-like complexes are able to recruit transcription regulators in every species studied. However, these regulators may vary depending on the organism or the target gene.

Chromatin state and histone marks

Besides binding histone tails or recruiting transcription regulators, as detailed above, the DREAM complex can also recruit proteins that modify the chromatin state or histone marks, which in turn affects transcription of its target genes (Figure 3). These mechanisms are illustrated below in invertebrates and in mammals.

Insulators are DNA elements that block the communication between an enhancer and a promoter. Dyson's lab has shown in *D. melanogaster* that the dREAM complex could co-operate with insulator-binding proteins to repress a subset of target genes by blocking enhancer sequence activity. Among these partners, Beaf-32 frequently binds to TSS close to dREAM-bound regions, and CP190, a co-factor of insulator complexes, can physically interact with dE2F2.[43] Therefore, insulator-binding proteins add another type of dREAM partners.

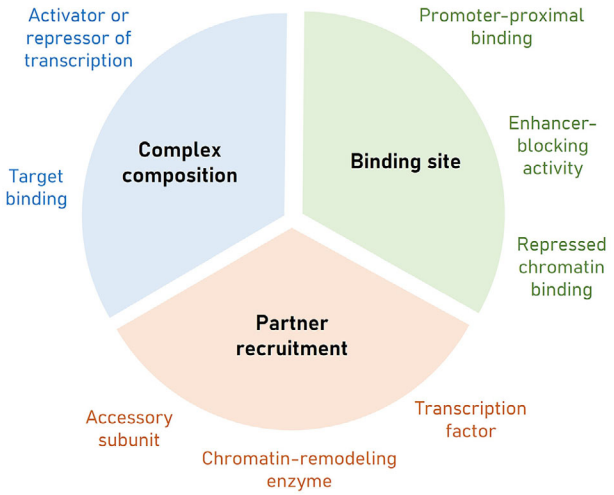

FIGURE 3 DREAM complexes modulate transcription through three mechanisms, which appear to be conserved even though different partners are involved according to the organism. (i) The DNA-binding subunits of the DREAM complex recruit it to their target sequences. Subunits also influence the activating or repressing action of the complex, as shown by the antagonism between Myb and Rbf1 subunits in D. melanogaster (blue). (ii) DREAMs regulate transcription by binding promoters or enhancers (green). (iii) DREAMs can also modulate transcription by recruiting external partners, such as accessory subunits, chromatin-remodeling enzymes, and other transcription factors (pink).

First identified as a G1 regulator in *C. elegans*,[55] LIN-36 was identified during an RNAi screen as regulators of a DREAM target reporter gene and is encoded by SynMuv class B genes.[56] It contains an atypical zinc-finger DNA-binding domain and interacts with DRM through LIN-35 at different target regions. Unsurprisingly, LIN-36 shares cell-cycle and cell-division gene targets with LIN-35. LIN-36 seems to function with DRM to recruit or maintain the repression-associated histone variant HTZ-1 in *C. elegans* on gene bodies. Consistently, around half of DRM targets characterized by this mark also appear to be a LIN-36 target.[56] A link between the *D. melanogaster* counterpart of HTZ-1, the H2A.Z variant, and the dREAM complex has also been found in *D. melanogaster*.[57] Therefore, DREAM-like complexes have been found to associate with some histone variants in invertebrates.

LIN-15B was identified in the same study as LIN-36 and also contains an atypical zinc-finger-DNA-binding domain and interacts with DRM through LIN-35 (p107/p130) at different target regions but it seems more specific to the germline. DRM associated with LIN-15B directs the MET-2 methyltransferase to the target genes to apply repressive H3K9me2 marks[56] and compact chromatin.[58] In *D. melanogaster*, the histone deacetylases HDAC1 homolog known as Rpd3 has also been identified as a dREAM complex partner.[5] It seems to be involved in the repression of the *hid* pro-apoptotic

gene.[59] Moreover, the Caf1/p55 dREAM subunit is part of the NURF (NUcleosome Remodeling Factor) complex, which suggests a possible interaction between those two complexes.[5] In human and mouse quiescent cells, most DREAM subunits interact with SIN3B, a scaffold protein known for assembling large repressive complexes containing HDACs,[60] which seems required to repress some of DREAM's targets.[61] Additionally, the MuvB core subunit RBBP4 (also known as RBAP48) interacts with HDACs and with the NURD (NUcleosome Remodeling and Deacetylase) complex.[62–64] Altogether, these data strengthen the role of chromatin accessibility in the DREAM-mediated regulation (Figure 3).

AN ESSENTIAL COMPLEX FOR VARIOUS BIOLOGICAL PROCESSES

Numerous genome-wide studies were led to determine the function of DREAM/MMB complexes after discovering dREAM in *D. melanogaster* and its homologs in *C. elegans* and mammals. Thanks to Gene Ontology analyses, these genome-wide studies identified processes involving DREAMs beyond the extensively described and reviewed role in the cell cycle progression.

A crucial role in the cell cycle

In mammals, the DREAM complex mainly binds to early or late cell cycle genes.[8,65] This result is not surprising since RB family proteins are regulators of the G1/S transition. The primordial role of DREAM in the control of the cell cycle is confirmed by loss-of-function studies and implies a role in developmental biology. LIN37 is essential to DREAM control of G0 entrance[66] and G1/S transition.[67] The role of LIN9 in regulating mitotic genes probably explains the embryonic lethality of null mutants.[68] This key role in cell proliferation and genomic stability is observed when LIN9 is deleted,[69] as it leads to mitotic defects and G2/M arrest.[9,17,70] Even before the dREAM complex description, Mip proteins were found along with Myb and Caf1/p55 in a database search to identify proteins that bind to replication origin-associated proteins in *D. melanogaster*, suggesting an ancestral role of these DREAM subunits in the control of replication.[6]

Mutually exclusive mammalian DREAM and MMB complexes described in the first part of our review are linked by their role in the cell cycle. In human cells, at G0 and early G1 phase, p107/p130-DP-E2F4-5 and the MuvB core associate into the DREAM complex[17] and contribute to repress E2F target genes such as *B-MYB*, cell cycle genes and *FOXM1*.[8,27,71] The kinetics that regulates the mutually exclusive association of Myb and RB/E2F in DREAM/MMB complexes and its impacts are described in Figure 1.

The tumor suppressor p53 is an important partner of mammalian DREAM/MMB. In stress conditions such as induction of DNA damage, activation of the p53 pathway induces the dissociation of B-MYB and the recruitment of p130/E2F4 to the MuvB core, forming and stabilizing the DREAM complex at promoters.[72,73] p53 also plays a crucial role in senescence, a stable cell cycle arrest state due to physiological aging or particular stress conditions.[74,75] Interestingly, the senescence of conditionally immortalized human breast fibroblasts is associated to the down-regulation of numerous genes, of which respectively 49%, 16% and 22% are targets of DREAM, RB-E2F, and MMB-FOXM1. Expression of *Myb*, *FOXM1*, and of a mutant *LIN52* encoding the non-phosphorylable LIN52-S28A is sufficient to bypass senescence of these cells.[76] Therefore, the mammalian DREAM/MMB and p53 interplay seems to extend over various activities, including coping with DNA damage and controlling senescence entry.

Regulation of programmed cell death

Although the mammalian DREAM complex seems to be mainly involved in cell cycle regulation, *D. melanogaster* dREAM may control a much larger spectrum of processes. Chromatin-immunoprecipitation studies revealed that around a third of all *D. melanogaster* gene promoters were bound by dREAM members,[38] suggesting a role for dREAM in controlling cellular processes beyond the cell cycle.

In *D. melanogaster*, the observation of a Myb-dependent apoptosis led Rovani et al. to investigate whether this cell death was directly controlled by Myb or a consequence of excessive proliferation. This study identified a cooperation between the pro-apoptotic *grim* gene and Myb in neural precursor cells at the posterior wing margin. Mip130 and Myb loss of functions lead to similar phenotypes and Myb seems epistatic to Mip130. Therefore, Myb-mediated cell death in this tissue most likely relies on its integration in the dREAM complex. Surprisingly, despite the often-admitted antagonistic role of E2F and Myb in the dREAM complex, dE2F2 is also involved in this process.[77] It thus seems that the conventional view of dREAM/MMB complexes may not account for the entire processes that can be encountered when focusing on their different roles. It remains undefined whether Myb and dE2F2 act in a unique complex or both MMB and dREAM complexes regulate cell death in a similar manner.

The dREAM/MMB regulation of apoptosis in *D. melanogaster* may even be more complex. Our team found that Rbf1 pro-apoptotic activity in the developing wing depends on the repression of the anti-apoptotic gene *buffy* and an activation of the pro-apoptotic gene *how*.[39] The MuvB core proteins Mip120 and Mip130 are required for this apoptosis and participate in the transcriptional regulation of *buffy* but not of *how*. In contrast, Myb seems to exert an antagonistic effect since its overexpression inhibits Rbf1-induced apoptosis, activates *buffy* transcription and decreases the transcriptional activation of *how* induced by Rbf1/dE2F2.[39] In a different tissue, that is, the eye-antenna disc, the dREAM complex containing Rbf1 can inhibit apoptosis through the repression of the pro-apoptotic *hid*.[59] Therefore, dREAM can have opposite roles in apoptosis, which seems to depend on the cells' proliferative state.

The implication of dREAM in the control of apoptosis is not limited to *D. melanogaster*. A screen designed to identify new programmed cell death genes in *C. elegans* revealed the role of the DP homolog

named *dpl-1*. Considering the partnership of mammalian DP with pRb and E2Fs, Reddien et al. investigated the role of their homologs, lin-35 and efl-1, in programmed cell death. This study revealed their pro-apoptotic role along with other DRM members: LIN-52 and LIN-37. Some DRM subunits, that is, LIN-53 and LIN-9, do not seem to be involved in this process, but we can hypothesize that DRM complex composition can differ depending on the target gene, as observed with dREAM in *D. melanogaster*.[78]

DREAM in gametogenesis

The SynMuv genes were identified in *C. elegans* as genes required for the development of reproductive organs.[79,80] In *D. melanogaster*, Korenjak et al. also proposed that dREAM may have a role in the reproductive system by regulating sex-associated targets, whose mis-expression could cause changes in cell fates.[4] This proposal was based on the fact that most dREAM members are conserved in both organisms and that dE2F2 is known to be required to express genes important in gametogenesis.[81] Consistently, dE2F2 mutants display fertility problems.[82,83]

Additionally, in *D. melanogaster*, tMAC (testis Meiosis Arrest Complex) is considered as a testis-specific kind of dREAM complex. This transcription regulation complex is composed of two dREAM subunits (Mip40 and Caf1-p55), three subunits homologous to dREAM elements, and two proteins that are not usually found in the dREAM complex.[84] DNA adenine methyltransferase identification (DamID) data revealed that dREAM and tMAC do not bind simultaneously the same promoters in the testis. It seem that dREAM represses genes in the testis, whereas tMAC activates spermatocyte-differentiation-governing genes by recruiting Mip40.[85] It remains to clarify if both complexes compete to bind some common components such as Mip40, if one can transform into the other and if both can coexist in the same cell during spermatogenesis. Interestingly, dREAM is also involved in oogenesis in *D. melanogaster*, since the absence of Mip120 causes an arrest of oogenesis associated with chromosome defects.[86] However, data on the role of dREAM in oogenesis are sparse. Whether this role depends on a regulation of cell cycle or not remains to be explored. Therefore, DREAM-like complexes seem to be involved in invertebrate reproductive organs.

Similar to the tMAC complex in *D. melanogaster*, a testis-specific complex seems to exist in mammals. This tMac-like was identified while studying a testis-specific paralog of LIN54 named MTL5 (Metallothionein-like 5) or Tesmin. MTL5 travels from cytoplasm to nucleus during spermatocytes meiosis in a LIN9-dependent manner. Immunoprecipitation associated with Mass Spectrometry (IP-MS), co-immunoprecipitation and proximity-dependent biotin labeling experiments showed that MTL5 interacts with A-MYB and all members of the MuvB core except LIN54 in mouse spermatocytes. Although DREAM is known for its role during mitosis, this testis-specific complex is involved in spermatocytes meiosis.[87,88]

CONCLUSION

DREAM complexes represent a highly conserved transcriptional regulator complex family, which may seem reminiscent of classic repressor complexes but display a much broader spectrum of action. Due to the diversity of mechanisms by which they regulate transcription, DREAM-mediated regulations are hard to predict. These complexes are composed of the MuvB core with added subunits that appear to be shared with other regulator complexes. The regulation of these interactions has only been nicely described for the mammalian DREAM/MMB complexes during cell cycling. Interestingly, animal models revealed that some of the MuvB core components are also part of other complexes, such as the tMac, which increases the level of regulation complexity. Studies of DREAM complexes will probably open new avenues to understand and to model the high complexity of sophisticated network regulations that now remain out of reach.

Due to their relatively low genetic complexity, *D. melanogaster* and *C. elegans* helped reveal new roles of DREAM/MMB complexes. Extending these studies to plants and other model organisms may lead to the discovery of new functions and regulations of these complexes that may or may not be ancestral. Among these roles, DREAM complexes regulate essential processes such as cell cycle, apoptosis and gametogenesis. Therefore, DREAM components, partners and regulators may be of great interest in the study of cancer biology. Consistently, the cell cycle regulators Myb and FOXM1 are often overexpressed in tumors. High levels of these proteins and their targets are associated with poor prognosis in many cancers.[89,90] Studying how DREAM complexes control proliferation and apoptosis could provide clues for targets and strategies for cancer therapies. Oddly enough, this aspect does not seem to have raised a strong interest and the potential role of mammalian DREAM/MMB in apoptosis regulation has not been explored yet.

AUTHOR CONTRIBUTIONS

Conceptualization: Marion Hoareau and Isabelle Guénal. Writing–original draft: Marion Hoareau. *Review and editing*: Aurore Rincheval-Arnold, Sébastien Gaumer, and Isabelle Guénal. *Figures*: Marion Hoareau.

ACKNOWLEDGMENTS

The authors thanks Pr Sébastien Bloyer and Pr Bernard Mignotte for helpful discussions. Parts of the figures were drawn by using pictures from Servier Medical Art or Wikimedia commons. Both are licensed under a Creative Commons Attribution 3.0 or 4.0 Unported Licenses. The authors' work on this subject was supported by the Ligue Contre le Cancer des Yvelines.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Hoareau, M., Rincheval-Arnold, A., Gaumer, S., & Guénal, I. (2023). DREAM a little DREAM of DRM: Model organisms and conservation of DREAM-like complexes. *BioEssays*, 2300125. https://doi.org/10.1002/bies.202300125