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综 述

一个功能丰富的转录调控分子——下游调控元件拮抗分子

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摘 要：下游调控元件拮抗分子(downstream regulatory element antagonist modulator, DREAM)与钙衰蛋白(Calsenilin)和钾通道辅助亚基(potassium channel interacting protein 3, KChIP3)，三者同属于神经钙感受器蛋白(neuronal calcium sensor, NCS)家族，由同一基因编码，但亚细胞定位不同且执行不同功能，其中DREAM定位于细胞核，有4个EF手型结构域(EF-hand-like motifs)能与钙离子可逆结合，诱导蛋白空间结构变化，结合到多种基因的下游调控元件(downstream regulatory element, DRE)位点发挥基因转录调节作用。DREAM在中枢神经系统(central nervous system, CNS)尤其是小脑皮层中高表达，通过调控*N*-甲基-*D*-天冬氨酸受体(*N*-methyl-*D*-aspartic acid receptor, NMDAR)影响学习和记忆，也参与阿尔兹海默症发病、炎症反应、血栓形成。随着更多DREAM新功能的发现，其在CNS中的生物功能受到更多关注。本文回顾DREAM的发现历史，分析该蛋白的结构功能特点、组织分布，讨论了近些年来在DREAM入核的调控、以及特有的钙依赖的基因调控机理方面研究进展，重点关注了DREAM -强啡肽原(prodynorphin, PDYN)-强啡肽(dynorphin, DYN)通路调节慢性疼痛的可能机制。

关键词：DREAM；转录调节；疼痛；DRE位点；钙信号
中图分类号：Q42；R741

DREAM: a multifunctional transcriptional regulator

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Abstract: DREAM (downstream regulatory element antagonist modulator), Calsenilin and KChIP3 (potassium channel interacting protein 3) belong to the neuronal calcium sensor (NCS) superfamily, which transduces the intracellular calcium signaling into a variety of activities. They are encoded by the same gene locus, but have distinct subcellular locations. DREAM was first found to interact with DRE (downstream regulatory element) site in the vicinity of the promoter of prodynorphin gene to suppress gene transcription. Calcium can disassemble this interaction by binding reversibly to DREAM protein on its four EF-hand motifs. Apart from having calcium dependent DRE site binding, DREAM can also interact with other transcription factors, such as cAMP responsive element binding protein (CREB), CREB-binding protein (CBP) and cAMP responsive element modulator (CREM), by this concerted actions, DREAM extends the gene pool under its control. DREAM is predominantly expressed in central nervous system with its highest level in cerebellum, and accumulating evidence demonstrated that DREAM might play important roles in pain sensitivity. Novel findings have shown that DREAM is also involved in learning and memory processes, Alzheimer's disease and stroke. This mini-review

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provides a brief introduction of its discovery history and protein structure properties, focusing on the mechanism of DREAM nuclear translocation and gene transcription regulation functions.

Key words: DREAM; transcriptional regulation; pain; DRE site; calcium signal

下游调控元件拮抗分子 (downstream regulatory element antagonist modulator, DREAM) 于 1999 年首次被发现，它以同源四聚体的形式与 *PDYN* 基因启动子附近的下游调控元件 (downstream regulatory element, DRE) 位点结合抑制基因转录 [1]。DREAM 蛋白序列上有 4 个 EF 手型结构域 (图 1)，是 EF 手型蛋白超家族中恢复蛋白 (Recoverin) 亚家族和神经钙感受器蛋白 (neuronal calcium sensor, NCS) 家族成员。DREAM 的 EF-1 核心区域的第 104 位半胱氨酸和第 105 位脯氨酸阻碍蛋白与 Ca^{2+} 的有效结合，被认为无 Ca^{2+} 结合功能；EF-2 既可与 Ca^{2+} 结合，也可以结合 Mg^{2+}；EF-3 和 EF-4 则与 Ca^{2+} 有高亲和力。利用物理化学方法分析纯化的 DREAM 蛋白结构表明，结合 Ca^{2+}、Mg^{2+} 后的蛋白高级结构发生改变，α- 螺旋含量显著增加 [2]。不同离子浓度和蛋白浓度条件下，DREAM 可能存在各种聚合形式，包括单体、二聚体和四聚体；无钙 DREAM 的空间架构灵活可变，利于不同生理功能的发挥；该蛋白序列的 N 端 1~65 氨基酸序列高度可变，与钙感受器家族其它成员几乎没有同源性，此区域包含了多个蛋白翻译后修饰位点，近来报道，钙调蛋白 (Calmodulin) 与 DREAM 的结合点位于该区 [3]，DREAM 高度可变的 N 端可能与其细胞定位和功能有关 [4, 5] (图 1)。

由不同实验室各自通过酵母双杂交方法筛选得到的早老素 2 (Presenilin 2, PS2) 结合蛋白钙衰蛋白 (Calsenilin)[6]、钾通道辅助亚基 (potassium channel interacting protein 3, KChIP3)[7] 与转录抑制因子 DREAM 都是由人染色体 2q11.1 上的同一个基因位点转录翻译而来，虽然蛋白序列相同，但蛋白的命名一直混乱没有统一。一般认为它们是不同名字的同一种蛋白，但各自亚细胞定位不同，生物功能不同 [8]。从公开发表的文献来看，分布于胞浆的一般叫做 Calsenilin，因为最初发现它能够与 PS2 的 C 端结合调节 γ- 分泌酶 (γ-secretase) 的酶活性，γ- 分泌酶是 β 淀粉样沉淀 (amyloid-β, Aβ) 生成的关键酶，阿尔兹海默症 (Alzheimer's disease, AD) 患者大脑皮层中 Calsenilin 表达量异常升高 [9]，*Calsenilin* 基因敲除小鼠大脑内的 Aβ 水平显著下降，海马齿状回区域神经元的长时程增强加强 [10]，近来研究显示 Calsenilin 也能与 PS1 的 C 端结合 [11]，另外，Choi 等人发现 Calsenilin 还是细胞凋亡调控关键分子 caspase-3 的底物 [12]。这些研究结果提示了 Calsenilin 通过与胞浆内不同蛋白结合发挥了不同的生物功能。KChIP3 是以细胞膜上的钾离子通道 Kv4 的辅助亚基的形式被发现，它与通道蛋白 N 端结合促进 Kv4.3 通道蛋白的上膜并调节通道的 I_{SA} 电流动力学，从而影响神经元的兴奋性。此外，不同细胞中

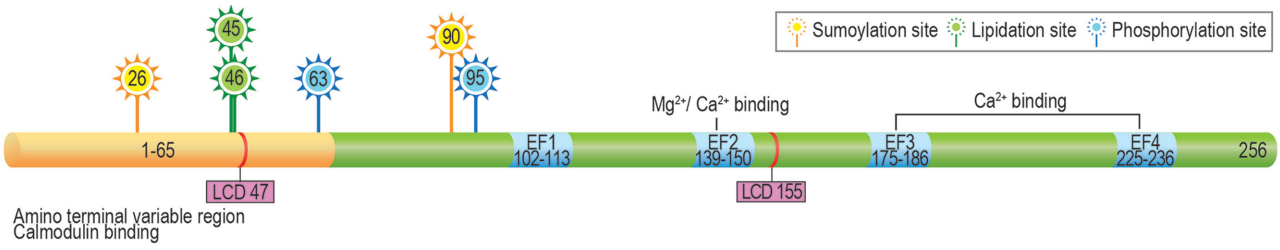

图 1. DREAM蛋白的一级结构

Fig. 1. Primary structure of DREAM protein. The full length of DREAM has 256 amino acid residues. N terminal of the protein (1–65 AA, yellow portion) is highly variable, in which most post-translational modification site located (flower marker); sumoylation is necessary for DREAM nuclear translocation; while lipidation and phosphorylation (flower marker) will facilitate DREAM functions outside nucleus; calmodulin interacts with DREAM through this N terminal region. C terminal of the protein (green portion) is highly homologous to other members of neuronal calcium sensor (NCS) proteins; it has four EF-hand motifs (blue portion) which bind Ca^{2+} or/and Mg^{2+} with varying affinity. Upon the binding with calcium, DREAM would adapt a reversible conformational change to fulfill its transcriptional regulatory function. The LCD is leucine residue-rich domain critical for DREAM-CREM interaction.

KChIP 亚型表达丰度不同，功能也并不完全重叠 [13, 14]。DREAM 最初是以 *PDYN* 基因转录抑制子的形式被发现，故推测 DREAM 发挥功能的场所在细胞核内部。但 DREAM、Calsenilin、KChIP3 三者胞内分布呈现动态变化趋势，并非一成不变。正由于上述原因，目前很多文献和基因 / 蛋白信息库，直接写成 DREAM/Calsenilin/KChIP3 形式，以显示三者的共性。本文中未明确细胞定位的该蛋白将以 DREAM/Calsenilin/KChIP3 形式统称，胞核定位的将以 DREAM 统称，胞浆定位的将以 Calsenilin 统称，胞膜定位的将以 KChIP3 统称。本综述主要讨论分析基因转录调节因子 DREAM 的结构特点，入核机制以及基因转录调节机制，也将描述关于 DREAM 在慢性疼痛中的角色，以及关于 DREAM/Calsenilin/KChIP3 通过钙依赖和非依赖形式参与中枢神经系统 (central nervous system, CNS)、血液系统、免疫系统以及胚胎干细胞发育调控等多方面的功能。

1 DREAM/Calsenilin/KChIP3表达分布

DREAM/Calsenilin/KChIP3 表达存在组织特异性。利用免疫组织化学法对大鼠大脑中的该蛋白表达分布进行检测，结果表明其在小脑颗粒层中高表达，在海马、视束、上丘、嗅球等处也有所分布。DREAM/Calsenilin/KChIP3 的表达分布模式与其已知的结合蛋白，如 Kv4.2、PS 的分布一致，与钙结合蛋白 D28K (calbindin D28K) 相反 [15]。甲状腺、胸腺、免疫细胞和生殖腺也可以检测到 DREAM/Calsenilin/KChIP3[16, 17]。

DREAM/Calsenilin/KChIP3 总体表达水平随发育过程逐渐增加。利用 *DREAM/Calsenilin/KChIP3* 基因敲除小鼠的研究表明，在胚胎期 (E12) 的脑、出生后发育期 (P20) 的外生发层 (external germinal layer, EGL) 及成年期皮层各部分都呈现表达高峰 [10]。

DREAM/Calsenilin/KChIP3 在细胞组织中的表达水平并非一成不变，而是受到不同生理病理条件的影响。例如，睡眠剥夺 72 h 后大鼠丘脑腹侧基底核内 DREAM/Calsenilin/KChIP3 水平显著下降 [18]；*Kv4.2* 基因敲除小鼠海马区 DREAM/Calsenilin/KChIP3 表达也显著降低 [19]；Lee 等人发现细胞 DREAM/Calsenilin/KChIP3 的水平与代谢型谷氨酸受体水平正相关 [20]。目前已知，DREAM/Calsenilin/KChIP3 是 NCS 家族中唯一具有钙依赖的基因表达调控功能的分子，其灵活多样的表达形式和空间结构提示该蛋白生物功能多样性和重要性。

2 DREAM转录因子的功能受到多种方式的调控

目前已知 DREAM/Calsenilin/KChIP3 蛋白生物活性的调控有如下几种方式：(1) 基因转录的差别剪切导致最终蛋白产物的不同 [8]；(2) N 端 63 位丝氨酸磷酸化与否决定了 caspase-3 是否对其切割，从而影响 DREAM/Calsenilin/KChIP3 的亚细胞定位和对细胞凋亡的调控 [21]；(3) N 端亮氨酸位点的棕榈酰化 (palmitoylation) 能促进 Kv4 钾离子通道上膜和通道的活性 [22]；(4) 被 PI3K 信号途径下游的激酶磷酸化后可改变 DREAM-DRE 位点的结合力 [23]；(5) 以钙依赖和非依赖两种方式和不同蛋白结合，这样一来，DREAM 除了调控含有 DRE 位点的基因如 *PDYN*，*FOS* 等，也能与其它蛋白合作间接调控更多其它基因的转录表达，例如，没有钙的情况下，形成 DREAM-CREB (cAMP responsive element binding protein)-CREM (cAMP responsive element modulator) 复合物，离开 CRE 位点，抑制靶基因转录；钙离子浓度升高后，DREAM 可以与 Calmodulin 结合，通过控制其它转录因子调控更多下游基因表达 [24] (图 2)；(6) DREAM/Calsenilin/KChIP3 自身反馈调节作用，比如表达对钙离子和 cAMP 不敏感的组成型激活 DREAM 突变体 (dominant active mutant DREAM, daDREAM) 转基因小鼠，其内源性 DREAM/Calsenilin/KChIP3 的表达下调 [25]。

DREAM 要行使基因转录调控功能的基本条件之一是出入胞核，这种转位与细胞类型、生物功能和处理条件有关，呈现动态分布功能转换状态模式 [26]。DREAM/Calsenilin/KChIP3 可以定位在胞膜、胞浆和胞核，用抗体免疫染色方法可以观察到，某些类型的细胞在基础生理状态下，荧光信号主要定位在胞浆，比如 SK-N-BE2(C) 细胞、HeLa 细胞、COS-7 细胞、Jurkat 细胞；原代培养的大脑皮层、海马神经元和小鼠脑组织的细胞亚组分分离样品用 Western blotting 检测则发现 DREAM/Calsenilin/KChIP3 主要定位于胞膜和胞浆 [27, 28]；Palczewska 等人用 DREAM 抗体和组蛋白抗体免疫双染急性分离的三叉初级感觉神经元，发现内源性 DREAM/Calsenilin/KChIP3 在胞核内富集 [29]。由于三叉神经节神经元负责各种感觉信息包括疼痛信息的处理，DREAM/Calsenilin/KChIP3 在核内富集提示该蛋白可能通过

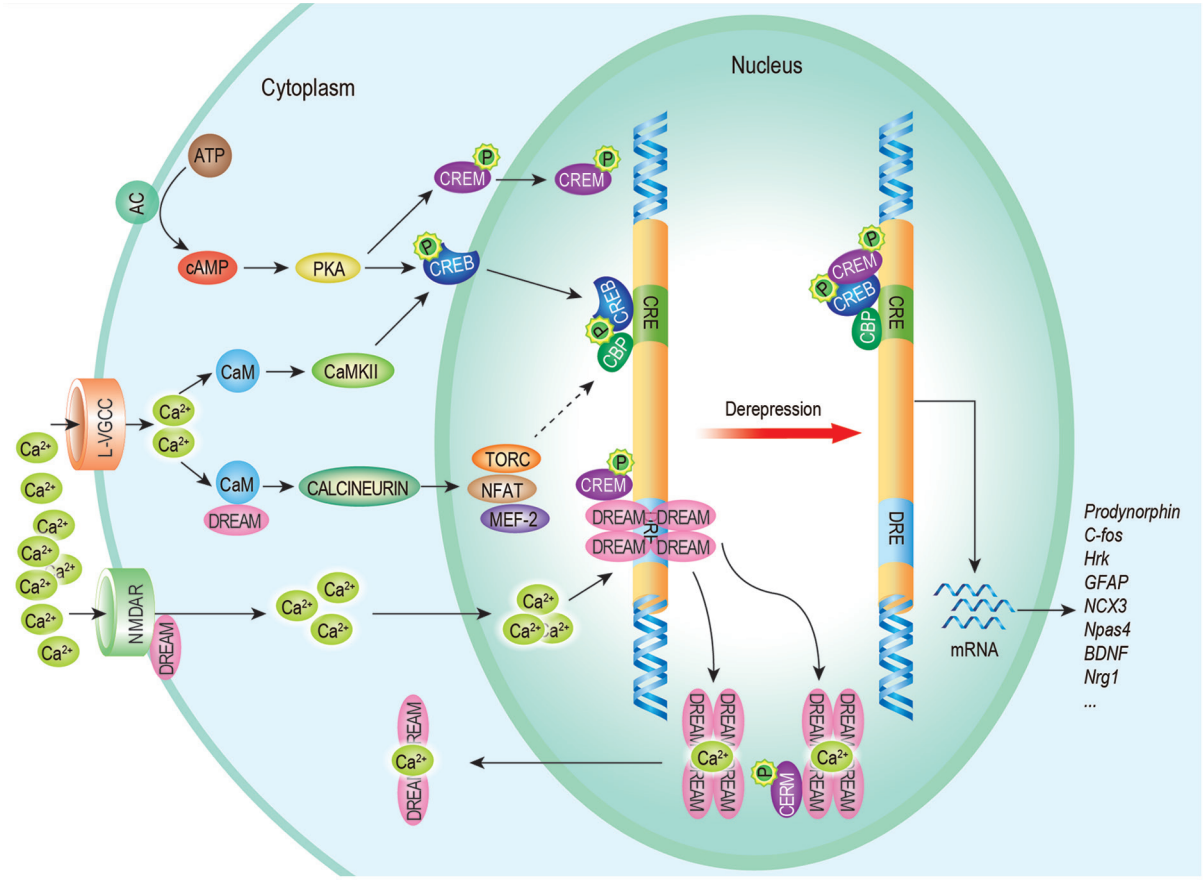

图 2. DREAM转录调控功能机制示意图

Fig. 2. Schematic diagram of mechanism by which DREAM carries on its transcriptional regulatory functions. Binding of tetramer DREAM on the DRE site on gene represses gene transcription; the repression is released upon elevated intracellular level of Ca^{2+} due to the conformational changes happened to the Ca^{2+} binding DREAM; the interaction between DREAM and phosphorylated CREM also disassembles the DREAM association with DRE. Phospho-CREB dependent activation through cAMP signaling cascade are also indicated. Additional transcriptional effects of the DREAM related co-factors are shown. Abbreviations: NMDAR: *N*-methyl-*D*-aspartate receptor; L-VGCC: L-type voltage gated calcium channel; AC: adenylyl cyclase; PKA: protein kinase A; CaM: Calmodulin; CaMK: Ca^{2+}/calmodulin-dependent protein kinase; CREM: cAMP responsive element modulator; CREB: cAMP response element binding protein; CBP: CREB-binding protein; NFAT: nuclear factor of activated T-cells; TORC: transducer of regulated CREB activity; MEF-2: myocyte enhancer factor-2.

调整新基因的转录表达以应对感觉神经元传递的信息刺激。在不同细胞系过表达 DREAM/Calsenilin/KChIP3 后的情况也各自不同，比如，PC12 细胞中荧光信号同时出现在胞浆和核内 [30]；HEK293 细胞中荧光信号则主要出现在细胞膜上。以上关于 DREAM/Calsenilin/KChIP3 亚细胞定位的研究结果提示，该蛋白在细胞内的分布因细胞类型和功能不同而有所差异，核内 DREAM 的水平可能随生理和病理条件改变而改变，例如，Alexander 等人研究 DREAM/Calsenilin/KChIP3 在记忆中的功能，结果显示情景恐惧记忆训练 6 h 后，小鼠海马神经元细胞膜上的 KChIP3 水平下降，核内 DREAM 水平显著上升，同时 DREAM 的直接靶基因 *Pdyn* 表达水平下调 [31]，虽然作者没有检测其它基因的表达变化，但目前已知恐惧刺激训练能诱导新基因的转录翻译 [32]，那么 DREAM 的转位入核提示其可能参与调控了记忆相关基因的转录；Link 等人研究生物钟周期分子生物机制时发现，DREAM-DRE 结合及解离规律与昼夜节律同步化，其靶基因的表达水平则与昼夜节律呈负相关 [33]，这些例子进一步说明了 DREAM 在细胞内的空间位置并非固定，这种空间位置变换需要出入核膜，但是 DREAM 序列本身不

含有核定位信号序列和经典的以亮氨酸富集为特征的蛋白出核信号序列，倘若外加药物刺激，如咖啡因、离子载体 A23187 或者毒胡萝卜素使细胞内钙离子浓度升高后，可能通过激活 CaMKII 激酶促进 DREAM 的核转位并抑制靶基因的转录；血清剥夺处理也能诱导人 H4 神经胶质瘤细胞的 DREAM 发生转位入核，具体机制不明 [34, 35]；因为 DREAM 运出胞核不受来普霉素 B (leptomycine B) 的抑制，推测 DREAM 的出核与出核受体 CRM1 无关；虽然 Palczewska 等人用胶体金染色发现 DREAM 和核孔复合物有共定位 [36]，但 DREAM 出入核是否通过核膜孔复合物或者特定的转运体，是否需要伴侣蛋白，尚需要更多的实验研究。

蛋白翻译后修饰影响 DREAM/Calsenilin/KChIP3 的细胞内定位。比如蛋白 N 端的豆蔻酰化和棕榈酰化是 KChIP3 细胞膜定位的条件之一 [22, 30]。PC12 细胞中，类泛素化修饰 (sumoylation, SUMO) 化的 DREAM 主要集中在细胞核组分中。三叉神经节神经元中，DREAM 和 SUMO 化反应关键酶 SUMO-1 共定位于细胞核 [36]。根据生物信息学方法预测分析和实验验证，DREAM 序列上有六个 SUMO 化位点，倘若 26 位和 90 位 SUMO 位点突变，DREAM 则无法入核 [36]。这些信息提示 SUMO 化是 DREAM 入核必要条件。另外，DREAM 序列上还含多个磷酸化位点 (图 1)，某些磷酸化位点影响 DREAM 的 SUMO 化修饰；某些磷酸化位点只影响细胞膜通道性能，和 DREAM 转录调节因子的功能无关，比如 G 蛋白耦联的受体激酶 GRK2 将 95 位的丝氨酸磷酸化后，仅影响 Kv4.2 钾离子通道的生理特性 [37]。由此看来，蛋白质翻译后修饰是 DREAM 发挥转录调节子功能的基础。

DREAM 通过钙依赖的空间构象改变的方式发挥转录调节作用。作为钙信号感应分子，胞内 Ca^{2+} 浓度直接影响 DREAM 高级结构。利用物理化学方法分析体外纯化的 DREAM，结果显示 Mg^{2+} 和 Ca^{2+} 离子与 DREAM 的 EF2，EF3 和 EF4 结构域结合后，干扰了四聚体 DREAM 复合物对 DRE 位点的结合，丧失转录抑制功能 [2, 4]，尽管目前已经了解到四聚体对 DREAM 转录调控的重要性，但是疑问尚存，比如，这种同源四聚体是否仅仅存在于胞核内？是否还存在其它形式的聚合体？它们与 DRE 位点是否有亲和性？所有表达 DREAM/Calsenilin/KChIP3 的细胞是否都是通过胞核内 DREAM 四聚体形式来调节基因表达？除了与基因转录调控区的 DRE 位点结合，DREAM 也可与环磷酸腺苷 cAMP 信号通路协同发挥基因表达调控作用，DREAM、CREB 和 CREM 通过各自的 LCD 结构域 (leucine-charged residue-rich domain) 相互作用，从而使 DREAM 从 DRE 位点上解离下来，去除转录抑制作用 [38, 39]。蛋白激酶 A (protein kinse A, PKA) 正是依赖上述过程调节 DREAM 的转录抑制功能 (图 2)。

由于 DREAM 在 CNS 中高表达，它与兴奋性神经递质谷氨酸的关系也有报道，研究显示谷氨酸能受体能不同程度地影响 DREAM 入核水平。激活 Müller 细胞的 NMDAR 导致 DREAM 胞核内富集，DREAM-DRE 结合受到抑制，细胞新基因大量表达 [40]。利用原代培养的皮层神经元研究显示特异性激活代谢型谷氨酸受体 mGluR5 显著诱导 DREAM 在细胞浆和胞核内的蛋白水平，但这种变化的生理意义尚待探索 [20]。在胶质细胞中，谷氨酸诱导 DREAM 移出细胞核，解除对 *Fos* 的转录抑制，这种作用可以被 mGluR5 特异的拮抗剂 MPEP 抑制，但不受 NMDAR 拮抗剂 MK 801 影响 [41]。

3 DREAM蛋白丰富的功能

3.1 DREAM蛋白发挥功能的方式

钙信号是重要的第二信使，DREAM 作为神经钙敏感蛋白能以钙依赖方式参与调节细胞的基本生理功能，也参与调节痛觉、视觉、学习、记忆，睡眠等脑高级功能 [42]。DREAM 主要通过两种途径发挥其功能。第一，与不同的蛋白结合。目前已知它能与超过 40 种不同的蛋白结合 (表 1)，这些蛋白与 DREAM 的物理结合有的依赖钙离子的存在，有的不需要钙离子，通过联合其它蛋白协同作用增加其调控范围，例如 DREAM/Calmodulin 以钙依赖方式激活钙调磷酸酶，诱导其下游的核因子 NFAT (nuclear factor of activated T-cells) 入核进而调控一系列下游基因表达 [43]。第二，基因转录调节因子。虽然最初 DREAM 是作为基因转录抑制因子被发现，但目前的共识是该蛋白既可以抑制也可以激活基因转录。表 2 罗列的是目前已知受到 DREAM 直接调控的基因，这些基因转录调节区域有若干正向或反向的 DRE 位点，如 *PDYN*、*Hrk*、*Fos*、*Npas4*、*Nr4a1*、*Mef2c*、*Junb*、*A20*、*Klf9* 等。

近年来利用组学方法和转基因动物研究发现了更多受 DREAM 调控的基因。比如，用表达谱芯片

表1. DREAM结合蛋白

Table 1. Proteins interacting with DREAM

Proteins	Functions	References
AP-2 complex subunit α-1	Protein transportation	[24]
Na^+/K^+-transporting ATPase subunit α-1	Na^+/K^+ exchanger	[24]
Active breakpoint cluster region-related protein	GTPase-activating protein	[24]
Glycogen phosphorylase, brain form	Glycogen metabolic reactions	[24]
Matrin-3	Nuclear matrix protein, maintain the stability of mRNA structure	[24, 61]
Trifunctional enzyme subunit, mitochondrial	Beta oxidation of fatty acids	[24]
Ubiquilin-4	Regulates proteasomal protein degradation	[24]
t-complex protein-1 subunit β	Protein folding	[24]
1,25-dihydroxyvitamin D_3 24-hydroxylase	Synthesis of vitamin D	[24]
Isocitrate dehydrogenase	Energy metabolism	[24]
NAD subunit a NAD-dependent deacetylase sirtuin 2	Myelination, activation of microglia and inflammatory reaction	[24]
ATPase ASNA 1	Insulin secretion, vesicular transport and apoptosis	[24]
Anionic trypsin-1	Metal binding	[24]
Cofilin-1	Actin assembly	[24]
GTPase Nras	GTP dependent small molecule protein, related to cell cycle, actin assembly, intracellular transportation	[24]
Transcription elongation factor B polypeptide 2	Gene transcription	[24]
Reticulon-1	May be involved in neuroendocrine secretion or in membrane trafficking in neuroendocrine cells ER protein	[24, 62]
Hippocalcin	NCS family	[24, 63]
Neurocalcin-δ	NCS family	[24, 64]
Hippocalcin-like protein 4	NCS, may be involved in calcium-dependent regulation of rhodopsin phosphorylation	[24]
Calmodulin	Calcium-binding protein is an important member of the calcium signaling pathway	[24]
Visinin-like protein 1	NCS	[24]
Complement C3	Complement system, involved in innate immunity	[24]
40 S ribosomal protein S18	Substrate of Caspase-3 and -7, Unknown function	[24]
Calcineurin subunit β type 1	Subunit of calcineurin	[24]
Contactin-1	Membrane protein, cell adhesion molecule	[24]
Ras-related protein Rab-3C	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-11B	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-14	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-6A	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-4B	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-2A	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-7A	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rab-1A	Small GTPase), GTP hydrolase	[24]
Ras-related protein Rab-10	Small GTPase, GTP hydrolase	[24]
Transforming protein RhoA	Cytoskeleton regulation	[24]
Ras-related C3 botulinum toxin substrate 1	Small GTPase, GTP hydrolase	[24]
Rho-related GTP-binding protein Rho G	GTP binding enzyme	[24]
Cell division control protein 42 homolog	Small GTPase, GTP hydrolase	[24]
Ras-related protein Rap-1A	Ras-related protein	[24]
ATP synthase subunit B	ATP-synthesizing enzyme subunit B	[24]
Mitochondrial fission 1 protein	ARCosome composition, promote mitochondrial fission	[24]
Peroxiredoxin-2	Antioxidative protein	[24, 65]
CLN3	Lysosomal function	[66]
NMDAR	Glutamate receptor and ion channel protein	[67]
PI3K classIβ	Involved in integrin-mediated platelet aggregation and fibrin clot formation	[56]

表2. DREAM直接转录调节的靶基因

Table 2. Target genes regulated by DREAM via DRE binding

Target genes	Functions	References
Pdyn	Pain regulation	[50]
Hrk	Participate in hematopoietic progenitor cell apoptosis	[68]
Gfap	Cytoskeleton	[60]
Ncx3, *Mid 1*, *Cacna1c*	Calcium homeostasis	[44]
Fra-2, *Crem*, *Aanat*	Circadian rhythm	[33]
Fos, *Npas4*, *Nr4a1*, *Mef2c*, *Junb*	Transcriptional regulation	[25]
Il-2, *Il-4*, *Ifng*	Inflammatory factors	[69]
GnRH	Regulate pituitary function	[70]
Bdnf	Neurotrophin family of growth factors	[71]
GCM1	Regulates differentiation of placental cytotrophoblasts	[72]
Cant1	Protein folding and degradation	[73]
Tg	Regulate thyroid function	[74]
A20	Involved in lung inflammatory response	[55]
Klf9	Regulate lymphocyte proliferation	[16]
PAX6, *NRG1*	Regulate the differentiation of human embryonic stem cells	[58]

分析 daDREAM 转基因小鼠小脑组织中表达变化的基因，变化倍数超过 1.15 倍的有 11 个基因，其中一个下游靶基因 *Mid1* 的表达下调，导致小脑组织结构异常运动功能受损 [44]；正常生理状态下三叉神经节神经元的 DREAM 富集在核内，用表达谱芯片分析福尔马林疼痛刺激对 daDREAM 小鼠三叉神经节神经元基因表达的影响，发现 481 个改变的基因中 31% 是核蛋白 [29]，这提示疼痛信号主要通过胞核内 DREAM 调控了疼痛相关基因表达变化。采用同样技术方法的研究还显示海马组织至少有 250 个基因的表达受到 daDREAM 的影响，其中 27% 是转录因子，如 *Npas4*、*Nr4a1*、*Mef2c*、*Junb* 和 *Fos* 等均表达下调；39% 是核蛋白。已知 DREAM 在海马中表达丰富，而海马是记忆和学习形成的重要区域，有活跃的基因表达活动 [45]，daDREAM 能通过调节一系列转录因子和核蛋白的表达，导致突触可塑性降低，小鼠的空间记忆能力下降；另外研究显示，过度激活的 DREAM 也能导致海马神经元细胞骨架蛋白架构变异，细胞形态异常 [46, 47]；相反，倘若 *DREAM* 基因敲除，小鼠的海马齿状回神经元长时程增强升高，记忆力增强 [10, 48]，同时 ATF6 (activating transcription factor 6) 活性由于 DREAM 的抑制解除而活性升高，使得亨廷顿病患者纹状体细胞的存活率上升 [49]。这些结果提示 DREAM 水平需要精确调控，过多或者过少都可能影响细胞的生理功能。值得注意的是芯片方法检测到的表达变化基因，既可能是直接受到 DREAM 的调控，也可能是间接调控。尽管如此，比较 DREAM 在 CNS 不同部位的基因表达谱，可以看出，受 DREAM 调控的基因数目和内容取决于细胞类型和功能，涉及的分子机理并不相同，该蛋白在脑高级功能中的作用表现复杂。

3.2 DREAM与疼痛

最初发现 DREAM 就是因为它结合在疼痛相关分子 *PDYN* 基因转录调控位点 DRE 上。阿片受体及内源性肽配体可调节疼痛，经典的阿片肽系统包括 μ、δ 和 κ 三种受体及其对应配体。在神经系统中，阿片肽受体及其配体在脊髓和外周神经中呈现广泛的分布，其中以与感觉信息特别是与疼痛相关的区域表达最为丰富。强啡肽原 (prodynorphin, PDYN) 经过酶的加工处理后形成具有活性的强啡肽 (dynorphin, DYN)，后者作用于 κ 受体，激活 K^+ 通道 (Kir3 和 Kv) 并提高神经元钾离子的电导，来抑制电压门控 Ca^{2+} 通道的开放，诱导神经元超极化从而抑制神经元的兴奋，发挥疼痛抑制作用 [50]，或通过 Gβγ 直接抑制囊泡的释放等方式来抑制神经元的兴奋从而阻断痛觉信号的上行通路起到镇痛作用。DREAM 在背根神经节和脊髓背角中的表达和点状分布模式与急性炎症疼痛的调节密切相关 [51]。*DREAM* 基因敲除小鼠的 PDYN 表达增强，小鼠对于急性热刺激、机械刺激、内脏痛、慢性神经疾病和炎症痛中都表现出低敏感性的特质，“No DREAM,

No Pain" 的结论由此被提出 [52]。

然而在慢性疼痛的调节方面，DREAM 的作用则表现得十分复杂。Zhang 等构建大鼠炎症痛模型，检测结果显示建模 2~6 h 后脊髓背角的 DREAM 蛋白在核内的表达增加，但细胞膜上的 KChIP3 表达也上升，并且会持续到 7 天以后 [51]。Long 等也在大鼠炎症痛模型中直接检测脊髓的 DREAM 和 PDYN 的 mRNA 和蛋白，结果显示脊髓内 DREAM 的 mRNA 水平升高，同时，细胞核内的 DREAM 蛋白水平也升高。但 PDYN 蛋白的表达增加，mRNA 并没有发生改变。在 DREAM 蛋白与 PDYN 之间并没有见到确切的相关性 [53]。Lilliehook 等在研究 *Calsenilin* 基因敲除的小鼠中并没有发现脊髓内 PDYN 水平升高，也没有发现基因敲除小鼠的疼痛行为发生明显改变 [10]。Rivera-Arconada 等研究显示 daDREAM 转基因小鼠脊髓及背根神经节 (dorsal root ganglion, DRG) 内的 PDYN 和脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 表达水平明显降低，外周炎症引起的痛觉过敏明显减弱。这可能是由于 DREAM 依赖的 BDNF 的表达水平下降引起的 [50]。综上所述，随着对 DREAM 研究的日益深入，出现了许多相互矛盾的结论，给诠释 DREAM 的生物功能带来不少困惑。

3.3 DREAM在其它非神经系统组织中的功能

DREAM 在甲状腺中高表达，以钙依赖方式抑制细胞周期素 D3 和 p27 调节甲状腺细胞的增殖 [54]。在肺部，DREAM 分子可以抑制锌指蛋白 (A20) 的表达，A20 是重要的炎症抑制因子，在炎症反应和肺部疾病中起重要作用 [55]。在免疫系统中，daDREAM 小鼠血浆中免疫球蛋白水平降低，同时通过抑制 *Klf9* 基因表达来促进 B 淋巴细胞的增殖 [16]。血小板是一种无核细胞，但细胞内有 DREAM 的 mRNA 和蛋白质，能激活磷脂酰肌醇激酶 (PI3K-Iβ) 活性，进而参与凝血与血栓形成的过程 [56, 57]。人胚胎干细胞的分化过程中，DREAM 诱导 *PAX6*、*NRG1* 表达，促进 CREB 的磷酸化作用控制神经元的发生 [58]。这些研究再次提示 DREAM 是一个功能丰富的分子。

4 总结与展望

对于 DREAM 的研究，在过去的十多年中已经有许多进展。一方面 DREAM 展示了更多令人惊讶的复杂多样的生物功能，进一步加深了人们对于其重要性的认识；另一方面，其发挥功能的细胞和分子机制仍然尚待阐明，距离其真正应用于临床疾病的治疗仍有很长的路要走。比如，既然在不同细胞或组织环境中 DREAM 作为转录调控因子控制的基因库不同，那么 DREAM 是如何实现这种差别？*DREAM* 基因敲除小鼠疼痛的敏感性表现出显著降低，而过表达 DREAM 的小鼠的空间记忆力下降，那么细胞是如何精确平衡 DREAM/Calsenilin/KChIP3 三者之间的动态关系？在病理状态下，如 AD 患者中 DREAM 如何影响 β 淀粉样肽段的形成？以 DREAM 为靶位点设计药物也许并非良策，针对疾病累及的主要组织或者细胞，阐明细胞类型相关的 DREAM 转录调控机制和下游分子更可能实现精准治疗。与 DREAM 异常相关的眼部疾病、肺部炎症性疾病、甲状腺疾病等治疗也应采取新的治疗思路。此外，一个重要的趋势是先前的研究大多关注神经元中的 DREAM，近年胶质细胞中所表达的 DREAM 与神经元中的差异受到一些神经科学家的关注 [59, 60]。这一发现也暗示胶质细胞在许多病理生理过程中起到重要作用。目前针对 DREAM 在多种生物功能过程中发挥作用的研究都处于起步阶段，并且专注研究 DREAM 的实验也只有寥寥几个，该分子如何成为临床疾病治疗的新靶点，以及胶质细胞在其中起到怎样的作用亟待引起更多学者的关注，投入更多力量进行深入的研究。

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参考文献

1 Carrión AM, Link WA, Ledo F, Mellström B, Naranjo JR. DREAM is a Ca^{2+}-regulated transcriptional repressor. Nature 1999; 398: 80–84.

2 Osawa M, Tong KI, Lilliehook C, Wasco W, Buxbaum JD, Cheng HY, Penninger JM, Ikura M, Ames JB. Calcium-regulated DNA binding and oligomerization of the neuronal calcium-sensing protein, calsenilin/DREAM/KChIP3. J Biol Chem 2001; 276: 41005–41013.

3 Gonzalez WG, Arango AS, Miksovska J. Amphiphilic residues 29-44 of DREAM N-termini mediate calmodulin:

DREAM complex formation. Biochemistry 2015; 54: 4391–4403.

4 Pham K, Dhulipala G, Gonzalez WG, Gerstman BS, Regmi C, Chapagain PP, Miksovska J. Ca^{2+} and Mg^{2+} modulate conformational dynamics and stability of downstream regulatory element antagonist modulator. Protein Sci 2015; 24: 741–751.

5 Lusin JD, Vanarotti M, Li C, Valiveti A, Ames JB. NMR structure of DREAM: Implications for Ca^{2+}-dependent DNA binding and protein dimerization. Biochemistry 2008; 47: 2252–2264.

6 Buxbaum JD, Choi EK, Luo Y, Lilliehook C, Crowley AC, Merriam DE, Wasco W. Calsenilin: a calcium-binding protein that interacts with the presenilins and regulates the levels of a presenilin fragment. Nat Med 1998; 4: 1177–1181.

7 An WF, Bowlby MR, Betty M, Cao J, Ling HP, Mendoza G, Hinson JW, Mattsson KI, Strassle BW, Trimmer JS, Rhodes KJ. Modulation of A-type potassium channels by a family of calcium sensors. Nature 2000; 403: 553–556.

8 Spreafico F, Barski JJ, Farina C, Meyer M. Mouse DREAM/calsenilin/KChIP3: gene structure, coding potential, and expression. Mol Cell Neurosci 2001; 17: 1–16.

9 Jin JK, Choi JK, Wasco W, Buxbaum JD, Kozlowski PB, Carp RI, Kim YS, Choi EK. Expression of calsenilin in neurons and astrocytes in the Alzheimer's disease brain. Neuroreport 2005; 16: 451–455.

10 Lilliehook C, Bozdagi O, Yao J, Gomez-Ramirez M, Zaidi NF, Wasco W, Gandy S, Santucci AC, Haroutunian V, Huntley GW, Buxbaum JD. Altered Abeta formation and long-term potentiation in a calsenilin knock-out. J Neurosci 2003; 23: 9097–9106.

11 Pham K, Miksovska J. Molecular insight of DREAM and presenilin 1 C-terminal fragment interactions. FEBS Lett 2016; 590: 1114–1122.

12 Choi EK, Zaidi NF, Miller JS, Crowley AC, Merriam DE, Lilliehook C, Buxbaum JD, Wasco W. Calsenilin is a substrate for caspase-3 that preferentially interacts with the familial Alzheimer's disease-associated C-terminal fragment of presenilin 2. J Biol Chem 2001; 276: 19197–19204.

13 Witzel K, Fischer P, Bähring R. Hippocampal A-type current and Kv4.2 channel modulation by the sulfonylurea compound NS5806. Neuropharmacology 2012; 63: 1389–1403.

14 Pruunsild P, Timmusk T. Subcellular localization and transcription regulatory potency of KCNIP/Calsenilin/DREAM/KChIP proteins in cultured primary cortical neurons do not provide support for their role in CRE-dependent gene expression. J Neurochem 2012; 123: 29–43.

15 Hammond PI, Craig TA, Kumar R, Brimijoin S. Regional and cellular distribution of DREAM in adult rat brain consistent with multiple sensory processing roles. Brain Res Mol Brain Res 2003; 111: 104–110.

16 Savignac M, Mellström B, Bebin AG, Oliveros JC, Delpy L, Pinaud E, Naranjo JR. Increased B cell proliferation and reduced Ig production in DREAM transgenic mice. J Immunol 2010; 185: 7527–7536.

17 Shinzato A, Lerario AM, Lin CJ, Danilovic DS, Marui S, Trarbach EB. Evaluation of downstream regulatory element antagonistic modulator gene in human multinodular goiter. Med Sci Monit Basic Res 2015; 21: 179–182.

18 Siran R, Ahmad AH, Abdul Aziz CB, Ismail Z. REM sleep deprivation induces changes of down regulatory antagonist modulator (DREAM) expression in the ventrobasal thalamic nuclei of Sprague-Dawley rats. J Physiol Biochem 2014; 70: 877–889.

19 Menegola M, Clark E, Trimmer JS. The importance of immunohistochemical analyses in evaluating the phenotype of Kv channel knockout mice. Epilepsia 2012; 53 Suppl 1: 142–149.

20 Lee J, Kim I, Oh SR, Ko SJ, Lim MK, Kim DG, Kim CH. Regulation of DREAM expression by Group I mGluR. Korean J Physiol Pharmacol 2011; 15: 95–100.

21 Choi EK, Miller JS, Zaidi NF, Salih E, Buxbaum JD, Wasco W. Phosphorylation of calsenilin at Ser63 regulates its cleavage by caspase-3. Mol Cell Neurosci 2003; 23: 495–506.

22 Takimoto K, Yang EK, Conforti L. Palmitoylation of KChIP splicing variants is required for efficient cell surface expression of Kv4.3 channels. J Biol Chem 2002; 277: 26904–26911.

23 Sanz C, Mellström B, Link WA, Naranjo JR, Fernandez-Luna JL. Interleukin 3-dependent activation of DREAM is involved in transcriptional silencing of the apoptotic Hrk gene in hematopoietic progenitor cells. EMBO J 2001; 20: 2286–2292.

24 Ramachandran PL, Craig TA, Atanasova EA, Cui G, Owen BA, Bergen HR 3rd, Mer G, Kumar R. The potassium channel interacting protein 3 (DREAM/KChIP3) heterodimerizes with and regulates calmodulin function. J Biol Chem 2012; 287: 39439–39448.

25 Mellström B, Sahun I, Ruiz-Nuno A, Murtra P, Gomez-Villafuertes R, Savignac M, Oliveros JC, Gonzalez P, Kastanauskaite A, Knafo S, Zhuo M, Higuera-Matas A, Errington ML, Maldonado R, DeFelipe J, Jefferys JG, Bliss TV, Dierssen M, Naranjo JR. DREAM controls the on/off switch of specific activity-dependent transcription pathways. Mol Cell Biol 2014; 34: 877–887.

26 Mellström B, Savignac M, Gomez-Villafuertes R, Naranjo JR. Ca^{2+}-operated transcriptional networks: Molecular mech-

anisms and *in vivo* models. Physiol Rev 2008; 88: 421–449.

27 Woo HN, Chang JW, Choi YH, Gwon AR, Jung YK, Jo DG. Characterization of subcellular localization and Ca^{2+} modulation of calsenilin/DREAM/KChIP3. Neuroreport 2008; 19: 1193–1197.

28 Zaidi NF, Berezovska O, Choi EK, Miller JS, Chan H, Lilliehook C, Hyman BT, Buxbaum JD, Wasco W. Biochemical and immunocytochemical characterization of calsenilin in mouse brain. Neuroscience 2002; 114: 247–263.

29 Benedet T, Gonzalez P, Oliveros JC, Dopazo JM, Ghimire K, Palczewska M, Mellström B, Naranjo JR. Transcriptional repressor DREAM regulates trigeminal noxious perception. J Neurochem 2017; 141: 544–552.

30 Venn N, Haynes LP, Burgoyne RD. Specific effects of KChIP3/calsenilin/DREAM, but not KChIPs 1, 2 and 4, on calcium signalling and regulated secretion in PC12 cells. Biochem J 2008; 413: 71–80.

31 Alexander JC, McDermott CM, Tunur T, Rands V, Stelly C, Karhson D, Bowlby MR, An WF, Sweatt JD, Schrader LA. The role of calsenilin/DREAM/KChIP3 in contextual fear conditioning. Learn Mem 2009; 16: 167–177.

32 Poplawski SG, Peixoto L, Porcari GS, Wimmer ME, McNally AG, Mizuno K, Giese KP, Chatterjee S, Koberstein JN, Risso D, Speed TP, Abel T. Contextual fear conditioning induces differential alternative splicing. Neurobiol Learn Mem 2016; 134 Pt B: 221–235.

33 Link WA, Ledo F, Torres B, Palczewska M, Madsen TM, Savignac M, Albar JP, Mellström B, Naranjo JR. Day-night changes in downstream regulatory element antagonist modulator/potassium channel interacting protein activity contribute to circadian gene expression in pineal gland. J Neurosci 2004; 24: 5346–5355.

34 Zaidi NF, Thomson EE, Choi EK, Buxbaum JD, Wasco W. Intracellular calcium modulates the nuclear translocation of calsenilin. J Neurochem 2004; 89: 593–601.

35 Ronkainen JJ, Hänninen SL, Korhonen T, Koivumäki JT, Skoumal R, Rautio S, Ronkainen VP, Tavi P. Ca^{2+}-calmodulin-dependent protein kinase II represses cardiac transcription of the L-type calcium channel α1C-subunit gene (*Cacna1c*) by DREAM translocation. J Physiol 2011; 589: 2669–2686.

36 Palczewska M, Casafont I, Ghimire K, Rojas AM, Valencia A, Lafarga M, Mellström B, Naranjo JR. Sumoylation regulates nuclear localization of repressor DREAM. Biochim Biophys Acta 2011; 1813: 1050–1058.

37 Ruiz-Gomez A, Mellström B, Tornero D, Morato E, Savignac M, Holguín H, Aurrekoetxea K, González P, González-García C, Ceña V, Mayor F Jr, Naranjo JR. G protein-coupled receptor kinase 2-mediated phosphorylation of downstream regulatory element antagonist modulator regulates membrane trafficking of Kv4.2 potassium channel. J Biol Chem 2007; 282: 1205–1215.

38 Ledo F, Carrión AM, Link WA, Mellström B, Naranjo JR. DREAM-alphaCREM interaction via leucine-charged domains derepresses downstream regulatory element-dependent transcription. Mol Cell Biol 2000; 20: 9120–9126.

39 Ledo F, Kremer L, Mellström B, Naranjo JR. Ca^{2+}-dependent block of CREB-CBP transcription by repressor DREAM. EMBO J 2002; 21: 4583–4592.

40 Chavira-Suárez E, Ramírez M, Lamas M. *D*-Serine/*N*-methyl-*D*-aspartate receptor signaling decreases DNA-binding activity of the transcriptional repressor DREAM in Muller glia from the retina. Neurosci Lett 2008; 432: 121–126.

41 Edling Y, Ingelman-Sundberg M, Simi A. Glutamate activates c-fos in glial cells via a novel mechanism involving the glutamate receptor subtype mGlu5 and the transcriptional repressor DREAM. Glia 2007; 55: 328–340.

42 Ross WN. Understanding calcium waves and sparks in central neurons. Nat Rev Neurosci 2012; 13: 157–168.

43 Boczek T, Lisek M, Ferenc B, Zylinska L. Cross talk among PMCA, calcineurin and NFAT transcription factors in control of calmodulin gene expression in differentiating PC12 cells. Biochim Biophys Acta 2017; 1860: 502–515.

44 Dierssen M, Fedrizzi L, Gomez-Villafuertes R, de Lagran MM, Gutierrez-Adan A, Sahún I, Pintado B, Oliveros JC, Dopazo XM, Gonzalez P, Brini M, Mellström B, Carafoli E, Naranjo JR. Reduced Mid1 expression and delayed neuromotor development in daDREAM transgenic mice. Front Mol Neurosci 2012; 5: 58.

45 Cho J, Yu NK, Choi JH, Sim SE, Kang SJ, Kwak C, Lee SW, Kim JI, Choi DI, Kim VN, Kaang BK. Multiple repressive mechanisms in the hippocampus during memory formation. Science 2015; 350: 82–87.

46 Mellström B, Sahún I, Ruiz-Nuño A, Murtra P, Gomez-Villafuertes R, Savignac M, Oliveros JC, Gonzalez P, Kastanauskaite A, Knafo S, Zhuo M, Higuera-Matas A, Errington ML, Maldonado R, DeFelipe J, Jefferys JG, Bliss TV, Dierssen M, Naranjo JR. DREAM controls the on/off switch of specific activity-dependent transcription pathways. Mol Cell Biol 2014; 34: 877–887.

47 Mellström B, Kastanauskaite A, Knafo S, Gonzalez P, Dopazo XM, Ruiz-Nuño A, Jefferys JG, Zhuo M, Bliss TV, Naranjo JR, DeFelipe J. Specific cytoarchitectureal changes in hippocampal subareas in daDREAM mice. Mol Brain 2016; 9: 22.

48 Fontán-Lozano A, Romero-Granados R, del-Pozo-Martín Y, Suárez-Pereira I, Delgado-García JM, Penninger JM, Carrión AM. Lack of DREAM protein enhances learning and memory and slows brain aging. Curr Biol 2009; 19: 54–60.

49 Naranjo JR, Zhang H, Villar D, González P, Dopazo XM,

Morón-Oset J, Higueras E, Oliveros JC, Arrabal MD, Prieto A, Cercós P, González T, De la Cruz A, Casado-Vela J, Rábano A, Valenzuela C, Gutierrez-Rodriguez M, Li JY, Mellström B. Activating transcription factor 6 derepression mediates neuroprotection in Huntington disease. J Clin Invest 2016; 126: 627–638.

50 Cheng HY, Pitcher GM, Laviolette SR, Whishaw IQ, Tong KI, Kockeritz LK, Wada T, Joza NA, Crackower M, Goncalves J, Sarosi I, Woodgett JR, Oliveira-dos-Santos AJ, Ikura M, van der Kooy D, Salter MW, Penninger JM. DREAM is a critical transcriptional repressor for pain modulation. Cell 2002; 108: 31–43.

51 Zhang Y, Li Y, Yang YR, Zhu HH, Han JS, Wang Y. Distribution of downstream regulatory element antagonist modulator (DREAM) in rat spinal cord and upregulation of its expression during inflammatory pain. Neurochem Res 2007; 32: 1592–1599.

52 Costigan M, Woolf CJ. No DREAM, No pain. Closing the spinal gate. Cell 2002; 108: 297–300.

53 Long I, Suppian R, Ismail Z. Increases in mRNA and DREAM protein expression in the rat spinal cord after formalin induced pain. Neurochem Res 2011; 36: 533–539.

54 D'Andrea B, Di Palma T, Mascia A, Motti ML, Viglietto G, Nitsch L, Zannini M. The transcriptional repressor DREAM is involved in thyroid gene expression. Exp Cell Res 2005; 305: 166–178.

55 Tiruppathi C, Soni D, Wang DM, Xue J, Singh V, Thippegowda PB, Cheppudira BP, Mishra RK, Debroy A, Qian Z, Bachmaier K, Zhao YY, Christman JW, Vogel SM, Ma A, Malik AB. The transcription factor DREAM represses the deubiquitinase A20 and mediates inflammation. Nat Immunol 2014; 15: 239–247.

56 Cho J. Downstream Regulatory Element Antagonist Modulator (DREAM), a target for anti-thrombotic agents. Pharmacol Res 2017; 117: 283–287.

57 Kim K, Tseng A, Barazia A, Italiano JE, Cho J. DREAM plays an important role in platelet activation and thrombogenesis. Blood 2017; 129: 209–225.

58 Fontán-Lozano A, Capilla-Gonzalez V, Aguilera Y, Mellado N, Carrión AM, Soria B, Hmadcha A. Impact of transient down-regulation of DREAM in human embryonic stem cell pluripotency: The role of DREAM in the maintenance of hESCs. Stem Cell Res 2016; 16: 568–578.

59 Bekar LK, Loewen ME, Cao K, Sun X, Leis J, Wang R, Forsyth GW, Walz W. Complex expression and localization of inactivating Kv channels in cultured hippocampal astrocytes. J Neurophysiol 2005; 93: 1699–1709.

60 Cebolla B, Fernández-Pérez A, Perea G, Araque A, Vallejo M. DREAM mediates cAMP-dependent, Ca^{2+}-induced stimulation of GFAP gene expression and regulates cortical astrogliogenesis. J Neurosci 2008; 28: 6703–6713.

61 Rayaprolu S, D'Alton S, Crosby K, Moloney C, Howard J, Duffy C, Cabrera M, Siemienski Z, Hernandez AR, Gallego-Iradi C, Borchelt DR, Lewis J. Heterogeneity of Matrin 3 in the developing and aging murine central nervous system. J Comp Neurol 2016; 524: 2740–2752.

62 Nepravishta R, Polizio F, Paci M, Melino S. A metal-binding site in the RTN1-C protein: new perspectives on the physiological role of a neuronal protein. Metallomics 2012; 4: 480–487.

63 Kumar KR. Mutations in hippocalcin and autosomal recessive dystonia: a role for perturbed calcium signaling? Mov Disord 2015; 30: 911.

64 Riessland M, Kaczmarek A, Schneider S, Swoboda KJ, Löhr H, Bradler C, Grysko V, Dimitriadi M, Hosseinibarkooie S, Torres-Benito L, Peters M, Upadhyay A, Biglari N, Kröber S, Hölker I, Garbes L, Gilissen C, Hoischen A, Nürnberg G, Nürnberg P, Walter M, Rigo F, Bennett CF, Kye MJ, Hart AC, Hammerschmidt M, Kloppenburg P, Wirth B. Neurocalcin delta suppression protects against spinal muscular atrophy in humans and across species by restoring impaired endocytosis. Am J Hum Genet 2017; 100: 297–315.

65 Voigt D, Scheidt U, Derfuss T, Bruck W, Junker A. Expression of the antioxidative enzyme peroxiredoxin 2 in multiple sclerosis lesions in relation to inflammation. Int J Mol Sci 2017; 18(4). pii: E760.

66 Chang JW, Choi H, Kim HJ, Jo DG, Jeon YJ, Noh JY, Park WJ, Jung YK. Neuronal vulnerability of CLN3 deletion to calcium-induced cytotoxicity is mediated by calsenilin. Hum Mol Genet 2007; 16: 317–326.

67 Wang K, Wang Y. Negative modulation of NMDA receptor channel function by DREAM/calsenilin/KChIP3 provides neuroprotection? Front Mol Neurosci 2012; 5: 39.

68 Sanz C, Mellström B, Link WA, Naranjo JR, Fernandez-Luna JL. Interleukin 3-dependent activation of DREAM is involved in transcriptional silencing of the apoptotic Hrk gene in hematopoietic progenitor cells. EMBO J 2001; 20: 2286–2292.

69 Savignac M, Pintado B, Gutierrez-Adan A, Palczewska M, Mellström B, Naranjo JR. Transcriptional repressor DREAM regulates T-lymphocyte proliferation and cytokine gene expression. EMBO J 2005; 24: 3555–3564.

70 Leclerc GM, Boockfor FR. Calcium influx and DREAM protein are required for GnRH gene expression pulse activity. Mol Cell Endocrinol 2007; 267: 70–79.

71 Rivera-Arconada I, Benedet T, Roza C, Torres B, Barrio J, Krzyzanowska A, Avendaño C, Mellström B, Lopez-Garcia JA, Naranjo JR. DREAM regulates BDNF-dependent spinal

sensitization. Mol Pain 2010; 6: 95.

72 Baczyk D, Kibschull M, Mellström B, Levytska K, Rivas M, Drewlo S, Lye SJ, Naranjo JR, Kingdom JC. DREAM mediated regulation of GCM1 in the human placental trophoblast. PLoS One 2013; 8: e51837.

73 Calì T, Fedrizzi L, Ottolini D, Gomez-Villafuertes R, Mellström B, Naranjo JR, Carafoli E, Brini M. Ca^{2+}-activated nucleotidase 1, a novel target gene for the transcriptional repressor DREAM (downstream regulatory element antagonist modulator), is involved in protein folding and degradation. J Biol Chem 2012; 287: 18478–18491.

74 Rivas M, Mellström B, Naranjo JR, Santisteban P. Transcriptional repressor DREAM interacts with thyroid transcription factor-1 and regulates thyroglobulin gene expression. J Biol Chem 2004; 279: 33114–33122.