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Minireview

CAMTAs: Calmodulin-binding transcription activators from plants to human

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Abstract **Recently, a novel family of calmodulin-binding transcription activators (CAMTAs) was reported in various eukaryotes. All CAMTAs share a similar domain organization, with a novel type of sequence-specific DNA-binding domain (designated CG-1). This domain could bind DNA directly and activate transcription, or interact with other transcription factors, not through DNA binding, thus acting as a co-activator of transcription. Investigations of CAMTAs in various organisms imply a broad range of functions from sensory mechanisms to embryo development and growth control, highlighted by the apparent involvement of mammalian CAMTA2 in cardiac growth, and of CAMTA1 in tumor suppression and memory performance.**

Keywords: Calcium; Calmodulin; Hypertrophy; Signal transduction; Transcription factor; Tumor suppression

1. Introduction

Transcription factors (TFs) play a crucial role in regulating every aspect of the organism's life cycle and are fit to respond to signals originating from within and without the organism. Ca^{2+} plays a key role in regulating gene transcription [1]. The mechanisms of Ca^{2+}-dependent transcription regulation are numerous and include various signal transducers, such as the superfamily of EF-hand Ca^{2+}-binding proteins (e.g. calmodulin, CaM) [1]. These regulate the activity of a number of transcriptional regulators such as the cAMP transcriptional activator CREB and its versatile co-activator CREB-binding protein CBP300 [2]. The expression of the mammalian *c-fos* gene is mediated by Ca^{2+} signals through two DNA regulatory elements, the CRE (cyclic-AMP-response element) and the SRE (serum-response element). Increase in nuclear Ca^{2+} concentration stimulates CRE-dependent gene expression, whereas elevation of cytosolic Ca^{2+} activates transcription via SRE [3]. Likewise, in plants different sets of genes are regulated by cytosolic and nuclear Ca^{2+} signals [4]. Thus, nuclear and cytoplasmic Ca^{2+} signals control transcription by distinct mechanisms. Ca^{2+} can also directly bind to and regulate certain TFs. The DREAM protein contains four EF-hand motifs and represses transcription [5], as DREAM affinity for DNA is reduced upon binding to Ca^{2+}. Similarly, a basic helix–loop–helix (bHLH) TF (AtNIG1) involved in salt-stress signaling in plants was also reported to directly bind Ca^{2+} [6]. In addition, certain TFs of the bHLH family were shown to directly bind CaM, thus inhibiting DNA-binding by masking the DNA-binding domain [7–9]. In plants, recent reports suggest the occurrence of other types of CaM-binding TFs including WRKY [10], Myb [11], and Calmodulin-binding Transcription Activators (CAMTAs) [12].

2. CAMTAs′ domain organization

The CAMTA proteins consist of multiple predicted functional domains, evolutionarily conserved in amino acid sequences, and organized in a conserved order (Fig. 1). The functional domains include: nuclear localization signals (NLS); CG-1, a unique DNA-binding domain (see details below); TIG, a domain implicated in nonspecific DNA contacts in TFs [13], and involved in protein dimerization [14,15]; ANK (ankyrin) repeats, which are present as tandemly repeated modules of about 33 amino acids in a large number of eukaryote proteins and viruses, and participate in protein–protein interactions [16–18]. In addition, CAMTAs contain a variable number of IQ motifs [12]. The IQ motifs consist of low complexity regions with the repetitive motif IQXXXRGXXX and are known to be associated with binding of CaM and CaM-like proteins [19,20]. Recent investigations in fly, mammals and plants, confirm the function of these domains in controlling gene expression, however, with interesting variations. Mapping of a Ca^{2+}-dependent CaM-binding domain in *Arabidopsis* AtCAMTA1 revealed a single high-affinity binding site ($Kd \sim 1.2$ nM) within an 18-amino acid region adjacent to the IQ motifs [12], predicting the occurrence of multiple CaM-binding sites with complex regulatory properties. Analysis of a rice CAMTA revealed a Ca^{2+}-dependent CaM-binding domain and 4 Ca^{2+}-dependent CaM-dissociation domains, equivalent to the IQ motifs (Ca^{2+}-independent), localized in the C-terminus [21]. Analysis of transcription regulation by a rice CAMTA using a synthetic promoter revealed that Ca^{2+}/CaM inhibited CAMTA-mediated transcription. In contrast, in *Drosophila* a Ca^{2+}-independent binding site for CaM was found within an IQ motif, and CaM binding to DmCAMTA is a prerequisite for DmCAMTA transcriptional activity [22]. CaM activation of DmCAMTA, however, is controlled by Ca^{2+} as evident in

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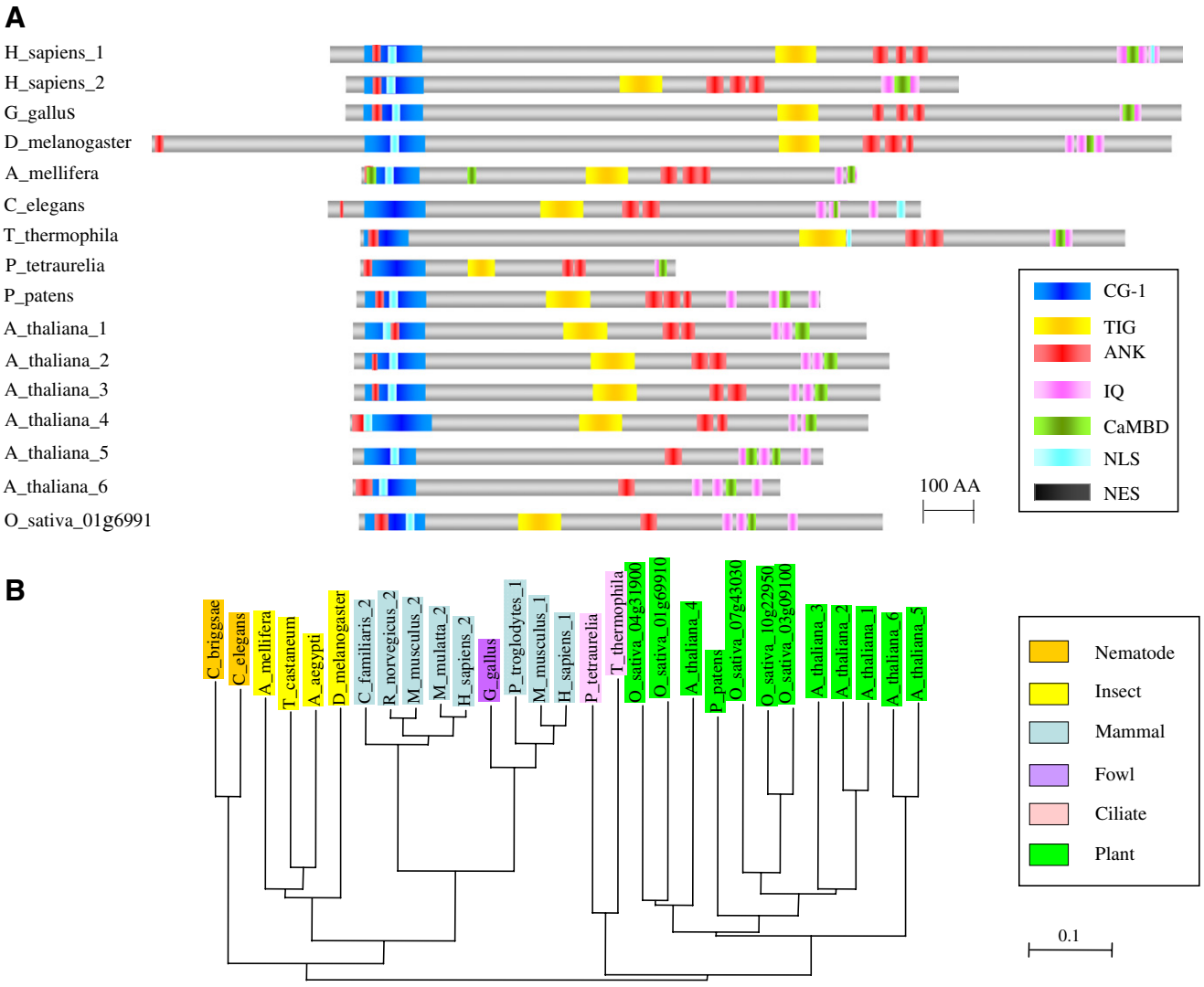

Fig. 1. Bioinformatics analysis of CAMTAs' domain organization, and phylogeny. (A) Domain organization: presentation of CAMTAs (drawn to scale) from multicellular and unicellular eukaryotes was obtained by NCBI/BLAST/CDART (Conserved Domain Architecture Retrieval Tool) at http://www.ncbi.nlm.nih.gov/Structure/lexington/lexington.cgi, based on NCBI http://www.ncbi.nlm.nih.gov/Entrez and http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi, Pfam (http://www.sanger.ac.uk/Software/Pfam) and DOUTfinder (http://mendel.imp.ac.at/dout/). CaM-binding domains (CaMBD) were specifically searched at http://calcium.uhnres.utoronto.ca/ctdb/flash.htm; Nuclear localization signals (NLS) were searched by a few programs: PredictNLS at http://cubic.bioc.columbia.edu/cgi/var/nair/resonline.pl, which searches for monopartite NLSs, exemplified by the SV40 large T antigen NLS (PKKKRRV), and bipartite NLSs, exemplified by the nucleoplasmin NLS (KRPAATKKAGQAKKKK); Motifscan at http://myhits.isb-sib.ch/cgi-bin/motif_scan; and the PSORT at http://www.psort.org/. Nuclear export signals (NES) were searched at http://www.cbs.dtu.dk/services/NetNES/. Transcription activation domains (TADs) were experimentally mapped to a region between the CG-1 and a transcription factor immunoglobulin (TIG)-like DNA-binding domain, domains in both AtCAMTA1 [12] and HsCAMTA2 [18], but as these could not be identified by bioinformatics analysis, they are not shown in Fig. 2. The CG-1 domain interacts with DNA *cis*-elements as described. In addition, the CG-1 domain of HsCAMTA2 was found to interact with the homeodomain of the Nkx2.5 TF (see Fig. 2), and acts as co-activator of transcription. Using the Superfamily bioinformatics program (http://supfam.mrc-lmb.cam.ac.uk/SUPERFAMILY/hmm.html), a previously unrecognized ANK domain was found within the CG-1 domain, suggesting a role for the CG-1 domain in protein-protein interactions. In fact, N-terminus ANK domains are found in almost all CAMTAs (except AtCAMTA5), suggesting that CAMTAs participate in multi-component complexes. The NLS were deduced by at least one search algorithm. NLS are localized to the N-terminus in most CAMTAs, with exceptions in some rice CAMTAs, which have an additional NLS at the C-terminus, as confirmed experimentally [21]. NLS is not detected in all CAMTAs: *Paramecium* CAMTA lacks an apparent NLS, but contains a putative NES in the N-terminus. In *C. elegans*, CAMTA contains both NLS and NES, localized to the C- and N-termini, respectively. Bioinformatics analysis of HsCAMTA2 detected NLS only in the N-terminus, but experimental evidence localized the NLS to the C-terminus, and an NES to the N-terminus [18]. (B) Phylogram tree: the tree was constructed using ClustalW (http://www.ebi.ac.uk/clustalw/), colored by phylogenetic classification: Nematodes, metallic gold; Insects, yellow; Mammals, light blue; Fowl, purple; Ciliates (unicellular protozoa), pink; Plants (monocotyledons, dicotyledons, and moss), green. CAMTA accession numbers:*Homo sapiens:* HsCAMTA1 (Q9Y6Y1), HsCAMTA2 (O94983); *Mus musculus*: CAMTA1 (CAM18835), CAMTA2 (CAM28144); *Gallus gallus*, red jungle fowl (XP_417530); *Pan troglodytes*, chimpanzee (XP_514346); *Canis familiaris*, dog (XP_546572); *Rattus norvegicus*, Norway rat (XP_213362); *Macaca mulatta*, rhesus monkey (XP_001117780); *Drosophila melanogaster*, fruit fly (ABI94369); *Apis mellifera*, honey bee (XP_001120489); *Aedes aegypti*, yellow fever musquito (EAT45641); *Tribolium castaneum*, red flour beetle (XP_968552);*Tetrahymena thermophila*, ciliate protozoa (XP_001011181); *Paramecium tetraurelia*, unicellular ciliate protozoa (CAK81933);*Caenorhabditis elegans*, nematode (NP_494796); *Caenorhabditis briggsae* (CAE67879); *Physcomitrella patens*, moss (gw1.188.72.1); *Arabidopsis thaliana*: AtCAMTA1 (Q9FY74), AtCAMTA2 (Q6NPP4), AtCAMTA3 (Q8GSA7), AtCAMTA4 (NP_176899), AtCAMTA5 (O23463), AtCAMTA6 (NM_112570); *Oryza sativa*: Os01g69910, Os03g09100, Os04g31900, Os07g43030, Os10g22950. The scale bar represents the number of changes per site.

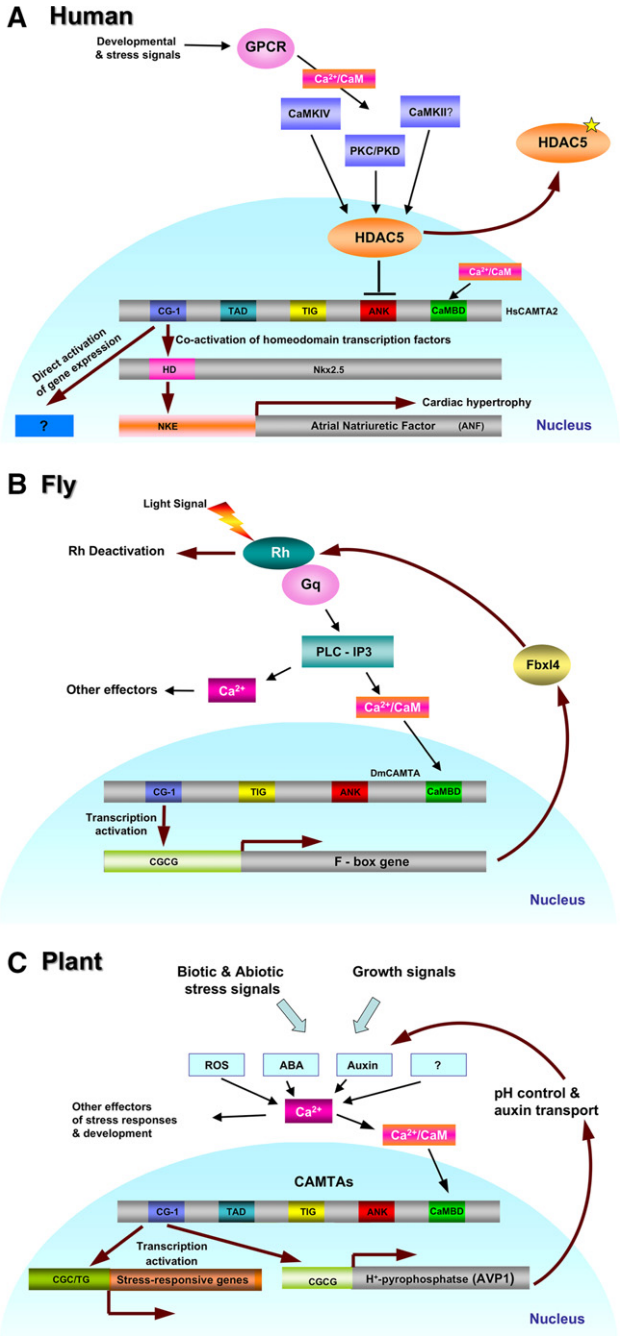

Fig. 2. Models for CAMTA-mediated signaling in human, fly and plants. (A) Human HsCAMTA2 mediates hypertrophic signaling: Cardiac growth is driven through multiple G protein-coupled receptors and protein kinases C and D (PKC/PKD) to class II Histone Deacetylase (HDAC5) [18,39,40]. HsCAMTA2 is repressed by association with HDAC5. Activation of PKC/PKD, leads to phosphorylation of HDAC5 (yellow star), and its nuclear export, thus relieving repression of CAMTA2. Cardiac hypertrophic growth is enhanced through the interaction of the CG-1 domain with the Nkx2.5 homeodomain and their binding to the Nkx2.5 response element (NKE) in the ANF promoter. HsCAMTA2 may have additional transcriptional targets, yet unidentified. (B) The fly DmCAMTA is essential in phototransduction: photoactivated rhodopsin (Rh) interacts with GTP-binding protein (Gq) triggering the phospholipase C (PLC) second messenger cascade (inositol 1,4,5 triphosphate and diacylglycerol). This results in the elevation of intracellular Ca^{2+}, due to the opening of cation channels, and in the depolarization of the photoreceptor cell [31]. Termination of the photoresponse occurs via deactivation of stimulated Rh, a process in which CAMTA is involved. Following CG-1 binding to the promoter of the F-Box gene *dFbxl4* at the CGCG site, CAMTA's transcriptional activity is stimulated via Ca^{2+}/CaM. The mechanism by which dFbXl4 deactivates Rh remains speculative; it may interfere with the association of Gq with Rh by directly binding to it or by mediating ubiquitination and degradation of Rh [22,41]. (C) Plant CAMTAs integrate stress and growth signals: plants respond and adapt to environmental stresses by multiple signaling pathways [42]. Ca^{2+} concentrations are transiently elevated, via increased Ca^{2+} influx in response to environmental stimuli, including abiotic (cold, heat, salt, drought, light, touch) and biotic (pathogens) stresses. Ca^{2+} transients are transduced by various types of Ca^{2+}-binding proteins including CaM, which affect numerous downstream targets and cellular processes. Auxin is a multifunctional plant hormone that plays a central role in growth and development, whose signal transduction is also mediated by Ca^{2+}/CaM [43]. The downstream targets of plant CAMTAs are mostly unknown, except for the *AVP1* gene encoding an H^+-pyrophosphatase (H^+-PPase), which generates proton gradients in endomembrane compartments with the breakdown of pyrophosphate (PPi). CAMTA binds to the promoter of *AVP1* via the DNA *cis*-element core CGCG, which triggers the proton gradient, essential to auxin uptake and efflux [26,33]. Thus, plant CAMTAs integrate developmental cues with stress-evoked cellular signals.

mutants defective in Ca^{2+} influx. There is less information about the interaction of mammalian CAMTA with CaM.

Nuclear localization signals are predicted in almost all CAMTAs, but there seem to be differences in the localization of NLS in CAMTAs of different organisms. Based on experimental data, mammalian CAMTA2 contains an NLS near the C-terminus and a nuclear export signal (NES) within the CG-1 domain [18]. In contrast, *Arabidopsis* CAMTA3 (AtSR1) contains an NLS in the CG-1 domain, as demonstrated by the localization of the CG-1 domain fused to GFP [23]. However, in a rice CAMTA (OsCBT) two NLS sequences were found, one in the N-terminal CG-1 domain and another in the C-terminal part [21]. Further experimental evidence revealed the occurrence of other functional domains including a transcription activation domain (TAD) in the *Arabidopsis* AtCAMTA1 [12], human HsCAMTA2 [18] and fly DmCAMTA [22]. Finally, proteins resembling CAMTAs were originally reported only in multicellular eukaryotes [12], however bioinformatics analysis of more recent databases revealed CAMTA-like proteins also in some unicellular eukaryotes including the ciliates *Paramecium tetraurelia* and *Tetrahymena thermophila* (Fig. 1).

3. CG-1: a unique and novel sequence-specific DNA-binding domain

The first hint that CAMTAs function as DNA-binding proteins came from the cloning of a cDNA encoding a partial plant protein that binds to a CGCG-containing DNA sequence [24]. Later, AtCAMTA3 (AtSR1) was reported to bind to the DNA consensus motif (G/A/C)CGCG(T/G/C) [23], and similar experiments with AtCAMTA1 [25] and OsCBT (a rice CAMTA) [21] extended the DNA-binding core sequence to CG(C/T)G. These results were confirmed by in vitro binding to authentic plant gene promoters containing CG(C/T)G-core *cis*-elements [21,23,26]. In plants, the CAMTA binding sequences include two known abscisic acid (ABA)–responsive

cis-elements (ABREs): the G-box ABRE [CACGTG(T/G/C)], and a related coupling element (ABRE-CE), (C/A)ACGCG(T/G/C), both of which have recently been reported to function as Ca^{2+}-responsive *cis*-elements [25,27]. Interestingly, the *Drosophila* DmCAMTA also binds to DNA sequences containing the CGCG-core motif [22]. An important DmCAMTA target gene containing this *cis*-element is the F-box gene d*Fbxl4*, which was shown to be required for deactivation of the G protein-coupled light receptor, rhodopsin [22]. A remaining open question is whether human CAMTAs bind directly to DNA, and if they do, to which DNA sequences. The conservation in DNA-sequence binding specificity is consistent with the relatively high amino acid sequence conservation of CG-1 domains [12]. However, there is yet no 3D structural model for the CG-1 domain and therefore its mode of interaction with DNA remains unresolved.

4. CAMTAs function as transcription activators and co-activators

Transcription activation domains (TADs) have so far been mapped in the *Arabidopsis* AtCAMTA1 [12] and human HsCAMTA2 [18]. Both TADs map to a region between the CG-1 and TIG domains. However, because there is little sequence homology among CAMTAs in this region, it is not known if all CAMTAs contain TADs. Further support of transcription activation by CAMTAs was obtained using reporter genes downstream of synthetic or native promoter sequences containing the CGCG-core motifs in plant protoplasts [21], and cell cultures [26]. The *Drosophila* DmCAMTA was also capable of activating transcription in vivo using the *dFbxl4* promoter containing a single CGCG-core binding site [22].

Mammalian CAMTA2 was reported to act as an activator of cardiac growth (hypertrophy), which is accompanied by transcriptional reprogramming of cardiac gene expression (Fig. 2). This activity is mediated by the interaction of HsCAMTA2, through its CG-1 domain, with the homeodomain of the Nkx2.5 TF. The latter binds to the NKE *cis*-element of the *atrial natriuretic factor* (*ANF*) gene, a cardiac-specific marker of hypertrophy. Functional mapping of the mammalian CAMTA2 domains suggests that in this physiological context there is no direct DNA-binding of the CG-1 domain to the NKE *cis*-element at the ANF promoter (NKE domain). In addition, while the CG-1 domain is sufficient for the association of CAMTA2 with Nkx2.5, activation of Nkx2.5-dependent transcription requires CG-1, TAD and TIG. Other protein–protein interactions occur via the mammalian CAMTA2 ANK domain. The function of the ANK domain in transcriptional regulation was demonstrated for the human CAMTA2, where it interacts with class II histone deacetylase (HDAC5) [18]. When this interaction occurs, it prevents the association of CAMTA2 with the Nkx2.5 homeodomain TF and consequently cardiac growth and remodeling genes are suppressed. This interaction is prohibited when histone deacetylase is phosphorylated in response to upstream signals from PKC and PKD, thus allowing cardiac gene activation by CAMTA2.

Therefore, the interaction of CAMTAs with co-activators and co-repressors, in addition to DNA *cis*-element binding, enables an expanded signal-dependent gene expression and regulation. Moreover, the CG-1 domain in *Drosophila* CAMTA mediates the dimerization of CAMTA proteins [28]. Therefore, in organisms with multiple CAMTAs the possibility of homo- and hetero-dimerization exists with further functional implications.

5. CAMTAs mediate responses to external stimuli including biotic and abiotic stresses

Arabidopsis CAMTA genes respond differentially and rapidly (within <15 min) to various environmental cues such as heat, cold, high salinity, drought, UV, and to signaling intermediates and phytohormones, such as H_2O_2, ABA, ethylene, salicylic acid, and methyl jasmonate [23]. The rapid response of *CAMTA* genes to these external chemical and physical stimuli suggests that they play a role in the cross-talk between multiple signal transduction pathways involved in stress tolerance.

In *Drosophila*, CAMTA is very abundant in photoreceptor cells (Fig. 2), and was indeed shown to stimulate the expression of the F-box protein, dFbxl4, resulting in rhodopsin deactivation [18]. Rhodopsin belongs to the class of G-protein-coupled receptors (GPCR) that convey extracellular stimuli by interaction with heterotrimeric G-proteins [29]. The tight regulation of the phototransduction pathway is essential for maintaining Ca^{2+} homeostasis, which involves light-induced Ca^{2+} influx through TRP channels, and Ca^{2+} extrusion by Na^+/Ca^{2+} exchange [30,31]. In this context, Ca^{2+} signaling, through CaM and DmCAMTA is essential for switching off the photo-stimulated system. Interestingly, Serial Analysis of Gene Expression (SAGE) reveals the prevalence of CAMTA2 transcripts in the developing and adult murine retina [32]. However, the function of CAMTA2 in the mammalian retina is currently unknown. If CAMTA is involved in the regulation of other GPCRs, and in other cell types, it may have a role in the regulation of the cell cycle, cellular growth, differentiation, and suppression of cell proliferation in response to signals other than light.

6. CAMTAs control growth and cell proliferation, and may function as tumor suppressors and in episodic memory performance

In plants, one of the identified targets of CAMTAs is the gene encoding *AVP1*, a H^+-pyrophosphatase [26]. In addition to maintaining vacuolar pH, the protein controls the transport of the main plant growth hormone auxin, and consequently controls auxin-dependent development [33]. AVP1 overexpression causes increased cell division at the onset of organ formation (hyperplasia) and increased auxin transport. Null mutants of *AVP1* have severely disrupted organ development and reduced auxin transport. Thus, plant CAMTAs may participate in growth control in response to stress by integrating responses to phytohormones and stress-evoked cellular signals (Fig. 2).

C. elegans contains two alternatively-spliced forms of CAMTA (T05C1.4). Silencing of this gene abrogates embryonic development (http://www.wormbase.org/db/gene/gene?name=WBGene00020251;class=Gene). A further example of the role of CAMTA in growth control is the case of mammalian CAMTA2, which functions as a co-activator of gene expression in cardiac hypertrophy, a process that may be triggered by a

variety of stress-responsive signaling pathways mediated by Ca^{2+} [34]. Over-expression of CAMTA2 stimulates hypertrophy and proliferation of cardiomycytes. However, although mammalian CAMTA1 and CAMTA2 are highly expressed in heart and brain [18], CAMTA2 does not show appreciable expression in the heart until after birth, whereas CAMTA1 is strongly expressed in the embryonic heart. It was therefore suggested that CAMTA1 mediates the developmental functions of TFs responsible for embryonic cardiac gene expression (e.g. Nkx2.5) [18].

A possible role of human CAMTA1 in cell proliferation and tumor suppression has recently been put forward by several research groups. A search for markers for neuroblastoma, the most common cancer in infants, revealed that expression of *CAMTA1*, a gene mapping to the 1p36 chromosomal region commonly deleted in neuroblastoma, can represent a powerful prognostic variable that may complement the predictive value of established risk factors in neuroblastoma [35]. Low *CAMTA1* expression was tightly associated with low overall survival probability. The prognostic value of *CAMTA1* expression was further supported by a genome-wide microarray expression study that identified *CAMTA1* as one of 47 top-ranked differentially expressed transcripts separating progressive from regressive neuroblastoma phenotypes [36]. The potential role of *CAMTA1* in tumor development is also supported by the findings of a recent loss of heterozygosity study in gliomas: a 1p minimal deleted region was identified that spans a region of 150 kb, where thus far the only gene mapped to that region is *CAMTA1* [37].

A recent study in an effort to identify genetic factors involved in human episodic memory performance [38] identified single nucleotide polymorphisms (SNPs) within the coding region of *CAMTA1* gene that were significantly associated with memory performance. Consistent with these findings, *CAMTA1* expression was shown to be enriched in memory-related human brain regions [38]. Hence, understanding the function and regulation of *CAMTA1* during embryogenesis and in the adult should give further insight into certain brain functions and types of tumors.

7. Conclusions and perspectives

The unique properties of CAMTAs, particularly the novel type DNA-binding domain (CG-1), should be regarded as excellent incentives to continue exploring these proteins in different organisms while addressing structural and functional questions. Identifying CAMTAs′ downstream target genes and interacting proteins are among the major tasks ahead. Such studies should provide important information to elucidate aspects of cardiac development and tumorigenesis, and consequently for improving diagnostic tools and therapies. In plants, *CAMTA* genes may serve as important targets for the improvement of stress tolerance in crops.

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