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REVIEW ARTICLE

Evolution and significance of CaM KMT- Calmodulin interaction- A journey of more than 40 years

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Abstract

The calmodulin (CaM) family serves as the primary calcium sensor. Upon receiving calcium signals, CaM binds calcium ions and regulates the activity of numerous effector proteins. In plants, several CaM-binding proteins have been identified and their roles are gradually becoming clear. CaM functions through interactions with short peptide sequences in target proteins, inducing conformational changes that modulate their activity in response to fluctuations in intracellular calcium. CaM-binding proteins, including transcription factors, ion channels and metabolic enzymes, enable plants to efficiently respond to environmental stresses and pathogen attacks. Studies employing genetic, molecular and biochemical approaches have provided valuable insights into CaM's role in regulating diverse targets to enhance stress resistance. Despite this progress, limited research has addressed CaM -lysine N-methyltransferase (CaM KMT), a crucial regulator of CaM. CaM KMT specifically trimethylates one specific lysine residue of CaM proteins, thereby influencing their function. This review summarizes research on CaM and its regulator CaM KMT, with a focus on Ca^{2+}/CaM-mediated regulation of plant responses to abiotic and biotic stresses, the role of lysine methylation in CaM function, the discovery and implications of CaM Lys-116 methylation and CaM KMT-mediated regulation across plants and animals. In conclusion, while substantial progress has been achieved in understanding CaM signalling, the role of CaM KMT remains underexplored. Future studies integrating structural, functional genomics and evolutionary approaches will be critical to clarify CaM KMT-mediated regulation, with implications for engineering stress-resilient crops.

Keywords: calmodulin; calcium signalling; CAM KMT; plant stress

Introduction

Calcium, in the form of Ca^{2+}, is an essential ingredient for a wide range of biological processes. Furthermore, aside from its crucial functions in maintaining the cell wall's structural integrity and the membrane system, it has been demonstrated to serve as an intracellular regulator in various areas of plant growth and development, including responses to stress (1). To prevent cellular energy metabolism from being harmed by high levels of Ca^{2+}, unstimulated cells maintain a low concentration of cytosolic Ca^{2+} at a nanomolar level (2). This is achieved by removing Ca^{2+} ions from the cytosol and transferring them to either the apoplast or the lumen of intracellular organelles like the vacuole or the endoplasmic reticulum (2, 3). Increased Ca^{2+} influx and quick Ca^{2+} efflux back to basal levels cause transient spikes in cytosolic Ca^{2+} concentrations in response to a range of stimuli, including light, abiotic stress factors, hormones or interactions with pathogens and symbionts (4). These Ca^{2+} transients are short-lived but act as crucial signalling events as cellular signals, causing alterations in cellular activities (5). Since Ca^{2+} functions as an intracellular intermediate in a wide range of stimuli, a key question in Ca^{2+} signaling is how this signal carrier transmits information from a perceived stimulus and regulates the specificity of cellular responses. The Ca^{2+} signatures are decoded, relayed and amplified by Ca^{2+}-binding proteins (Ca^{2+} sensors), which then control downstream signal transduction and trigger cellular responses. Ca^{2+} sensors encompass CaMs and CaM-like proteins (CMLs), Ca^{2+}-dependent protein kinases (CDPKs or CPKs) and Ca^{2+}/CaM-dependent protein kinase (CCaMK), as well as calcineurin B-like proteins (CBLs) (6). There is another gene known as *CAMTA* (CaM -binding Transcription Activator) gene, which encodes a transcription factor that binds calmodulin in a calcium-dependent manner, regulating gene expression in response to calcium signals. In the CaM - CaMKMT complex, CAMTA modulates downstream stress and developmental responses by linking calcium sensing (via CaM) to transcriptional regulation (7, 8). Prior research has documented several studies associated with CaM genes. In *Arabidopsis thaliana AtCaM1* was found to positively regulate ROS production, yellowing of leaves and ABA responses (9). *AtCaM1* and *AtCaM4* confer salt resistance by promoting nitric oxide (NO) accumulation (10). Transgenic rice that has been genetically modified to express higher levels of the CaM gene *OsCam1-1* exhibits greater tolerance to salt stress and dehydration stress compared to wild-type rice (11, 12).

Numerous studies have been published that have explored various aspects of Ca^{2+} signaling in plants (13). This update specifically highlights the significance of calmodulin-lysine N-methyltransferase (CaM KMT) in the process of Ca^{2+} signaling in plants and the evolution of CaM and CaM KMT interaction. Specifically, it addresses the potential involvement of CaM KMT in the trimethylation of a lysine residue located at position 116 of CaM. CaM protein sequences are highly conserved throughout the species and this lysine residue is present in all the reported CaM. Plant CaM proteins show a lot of conservation in their amino acid sequences, especially in the four EF-hand motifs that help them bind to Ca^{2+}. These conserved residues, rich in aspartate and glutamate, are essential for CaM to maintain its fundamental function as a Ca^{2+}sensor (14). The conservedness in amino acid residues between monocots and dicots suggests that CaM-mediated signalling is a key mechanism to govern how plants grow, develop and deal with stress. Fig. 1 depicts the conserved CaM protein sequences derived from different species. The conservation of this lysine-116 residue position in CaM across various species highlights the significance of investigating the impact of lysine methylation on stress responses. Further investigations in this area are necessary for future research.

Ca^{2+}/CAM - mediated regulation in plant response to different stresses

Hydrogen peroxide (H_2O_2), hydroxyl radical (.OH), singlet oxygen ($^1O_2$) and superoxide anion (O_2^-) are examples of reactive oxygen species (ROS), which are produced in many physiological processes and serve as a class of secondary messengers (15, 16). Additionally, the production of H_2O_2 during oxidative burst relies on the continuous influx of Ca^{2+}(17). This influx directly activates NADPH oxidase, which is located on the plasma membrane and contains an EF-hand, as well as NAD kinase (NADK), which binds to CaM and supplies the NADP cofactor required for ROS generation via NADPH oxidase (18 - 1). Early research on heat stress (HS) revealed that the amount of CaM in maize coleoptiles grew dramatically during HS and was impacted by the Ca^{2+} level, indicating a role for both Ca^{2+} and CaM in heat stress-induced thermotolerance (22). In a study, a rapid elevation in intracellular calcium levels was reported within one minute of exposing wheat plant to a high temperature of 37 ℃, which in turn promoted the expression of both CaM mRNA and protein in response to HS (23). Additionally, the administration of exogenous Ca^{2+} stimulated the expression of HSP26 and HSP70. The Arabidopsis *atcam3* loss-of-function mutant exhibited a significant reduction in thermotolerance during a 50 min incubation at 45 ℃ (24). HS was observed to cause two distinct phases of cytosolic Ca^{2+} fluctuations and this characteristic pattern was also observed in the expression of *OsCaM1-1* triggered by HS. When *OsCaM1-1* was overexpressed in *Arabidopsis*, it led to an increased ability to tolerate high temperatures. The researchers discovered that the cytosolic Hsp70 protein in maize can bind to CaM when Ca^{2+} is present. This binding can then decrease the activity of CaM-dependent NADK in a manner that depends on the quantity of the Hsp70 protein (25). In early studies, it was discovered that DgHsp70, a protein similar to cytosolic Hsp70 found in orchard grass (*Dactylis glomerata*), may bind to AtCaM2 in the presence of calcium ions (Ca^{2+}) (26). This binding of Ca^{2+}/CaM was observed to reduce the ATPase and foldase activities of DgHsp70. Another study in cold stress discovered that exposure to cold shock and wind triggers the occurrence of Ca^{2+} transients in both the cytosol and nucleus of transgenic tobacco seedlings expressing aequorin. Additionally, the expression of *NpCaM-1* is stimulated by both cold shock and wind (27). Reduced levels of COR transcripts were seen in *Arabidopsis* plants overexpressing *CaM3*, suggesting that CaM may act as a suppressor of expression of genes activated by cold (28). Previous studies discovered that the Ca^{2+}/CaM-regulated receptor-like kinase CRLK1, which is mostly found in the plasma membrane, has a role in cold tolerance (29). CRLK1 possesses two CaM-binding sites, one located in the N-terminus and the other in the C-terminus. The affinity of both sites for Ca^{2+}/CaM is 25 nM and 160 nM, respectively. Therefore, by affecting the MAP kinase cascade, the Ca^{2+}/CaM - regulated CRLK1 protein may control the process of cold adaptation in plants. It is also suggested that other CaM-binding kinases play a part in cold adaptation. Low temperature and salt stress were found to increase *PsCCaMK* expression in pea (*Pisum sativum*) roots (30). Additionally, it was discovered that cold shock increased the activity of the Ca^{2+}/CaM-dependent NADK (31). *Arabidopsis thaliana AtCaM15*, also known as *AtCML18*, which is located in the vacuolar lumen and forms a connection with the

Fig. 1. CaM protein sequences from *Oryza sativa* (OsCaM), *Arabidopsis thaliana* (AtCaM), *Glycine max* (GmCaM), *Nicotiana tabacum* (NtCaM), *Capsicum annum* (CaCaM), *Zea mays* (ZmCaM), *Rattus norvegicus* (RnCaM), *Homo sapiens* (HsCaM), VU1 and VU3 were aligned using MEGA X and formated through GeneDoc. Yellow colour indicates 100 % similarity for all sequences, green color indicates 75-100 % similarity, grey color indicates 50-75 % similarity and red box indicate lysine residue at position 116 except VU3.

C-terminus of *AtNHX1* (32). The interaction between *AtCaM15* and *AtNHX1* is influenced by both calcium ions (Ca^{2+}) and pH levels. The interaction between AtCaM15 and AtNHX1 alters the exchanger's selectivity for sodium ions (Na^{+}) and potassium ions (K^{+}) by reducing the rate of sodium ion (Na^{+}) exchange for hydrogen ions (H^{+}). The existence of Ca^{2+}-pH-dependent signalling elements in the vacuole, evidenced by the interaction between AtCaM15 and AtNHX1, contributes to the modulation of plant responses to salt stress. Early studies investigated metal toxicity responses and demonstrated that Ca^{2+}/CaM plays a role in radish (*Raphanus sativus* L.) responses to Cd^{2+} toxicity during the early stages of seed germination (33). Transgenic plants possessing a truncated version of *NtCBP4*, excluding the C-terminal region with the CaMBD and part of the anticipated cyclic nucleotide-binding domain, exhibited increased resistance to Pb^{2+} and decreased Pb^{2+} buildup. Additionally, when the *AtCNGC1* gene, which is like *NtCBP4* in *Arabidopsis*, was mutated to lose its function, it also led to Pb^{2+} tolerance.

The results demonstrate that the association of CaM is essential for the proper operation of both AtCNGC1 and NtCBP4 in heavy metal transport (34). GmCaM4 and GmCaM5, two distinct isoforms of the protein CaM in soybean, are quickly activated by fungal substances that stimulate a response (35). When *GmCaM4* or *GmCaM5* is overexpressed in tobacco, *Arabidopsis* and soybean, it causes the development of spontaneous lesions, activates a set of genes related to systemic acquired resistance (SAR) and improves the ability to resist a wide range of pathogens, including the oomycete *Phytophthora sojae*, as well as two necrotrophic fungal pathogens, *Alternaria tenuissima* and *Phomopsis longicolla* (35-37). Silencing the expression of *NtCaM13*, a gene like *GmCaM4* and *GmCaM5*, led to increased vulnerability to harmful necrotrophic pathogens in tobacco. This indicates that *NtCaM13* plays a beneficial function in the fundamental defense against necrotrophic diseases (38). The involvement of Pepper (*Capsicum annuum*) *CaCaM1* in the formation of ROS and nitric oxide (NO) has been postulated. These molecules have a crucial role in regulating cell death and defense responses (39). The silencing of *CaM2* and *CaM6* in tomato leads to changes in the expression of defense-related genes and significantly decreases resistance to tobacco rattle virus (TRV) and the oomycete disease *Pythium aphanidermatum* (40).

Lys methylation-involved regulation

Methylation is a common biochemical event in cells that involves the transfer of a methyl group from S-adenosylmethionine (AdoMet) to different substrates. It is catalysed by methyltransferases (MTases) and ranks as the fourth most common post-translational modification in terms of abundance. There are over 26041 known methylation sites in around 9705 proteins (statistics from iPTMnet v6.2, iPTMnet Statistics (udel.edu)), January 2024 (41). Methylation can occur on nitrogen, carbon and sulfur atoms of protein residues and can affect the hydrophobicity and bulkiness of lysine side chains of eight residues, namely arginine, asparagine, aspartate, cysteine, glutamate, glutamine, histidine and lysine, together with the terminal α-amino and α-carboxyl groups (42). Protein methylation is an essential component of cellular life and can lead to unique biological outcomes. Methylation removes a proton from the ε-amino group of lysine, decreasing its hydrogen-bonding potential (43, 44). It also enhances the hydrophobicity and bulkiness of the lysine side chain to a moderate extent. Methylation affects various cellular processes, including transcription, protein synthesis, signal transduction and metabolism (45, 46). Unlike acetylation and other modifications, methylation does not alter the overall charge of the residue (Fig. 2) (44, 47). Therefore, the alterations in the physicochemical characteristics of lysine residues induced by methylation are relatively unnoticed, which accounts for the challenges in comprehending the biological effects of this modification in non-histone proteins (42). Since the beginning of the 21st century, several non-histone proteins have been found to be

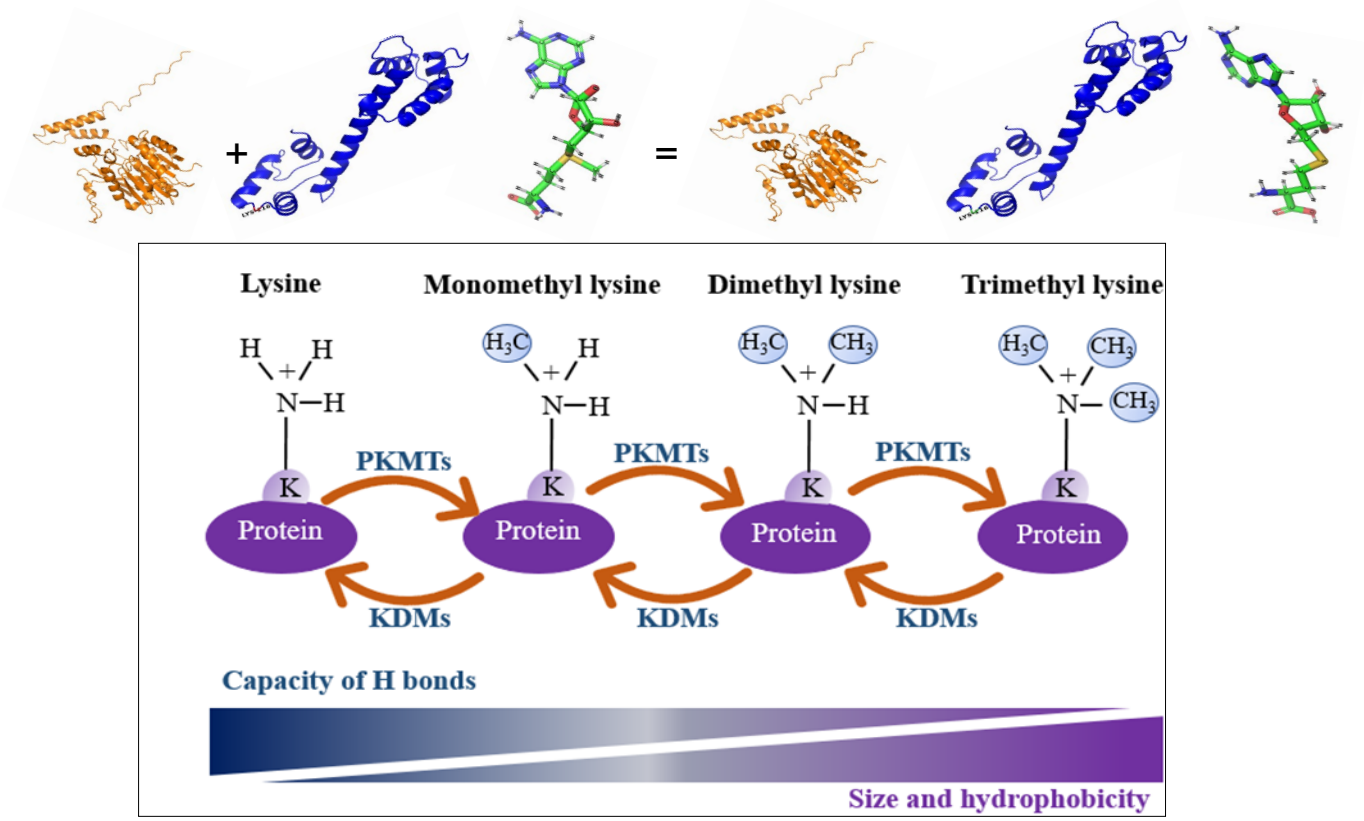

Fig. 2. Schematic diagram representing process of calmodulin methylation.

regulated by lysine methylation. This modification has been shown to control various cellular processes such as transcription, protein synthesis, signal transduction and metabolism (48). It affects protein-protein and protein-nucleic acid interactions, protein stability and enzyme activity (43, 45). Protein lysine methyltransferase (PKMTs), which methylates lysine residues, are classified into two families: the seven-beta-strand (7BS) superfamily and the SET domain family. 7BS proteins exhibit a characteristic structural fold known as the Rossmann-like fold. This fold is composed of a seven-stranded β-sheet connected to α-helices, along with other structural components that indicate the wide range of substrates that these enzymes can interact with (42).

Discovery of CaM 115-Lys methylation and its effect

Most CaMs have a notable characteristic of post-translational methylation at Lysine-116 (L-116), as reported by (49). CaM KMT catalyzes the transfer of a methyl group (-CH_3) from S-adenosyl methionine (SAM), a common methyl donor in cellular reactions, to the nitrogen atom of the lysine side chain in CaM. The methyl group is attached to the nitrogen of the lysine residue, converting it from an amine group (-NH_2) to a methylated amine group (-NH-CH_3). The methylation reaction results in the formation of S-adenosyl homocysteine (SAH) as a byproduct, along with the methylated CaM. SAM is consumed in the process and SAH is released as a waste product. The process of CaM methylation is depicted in Fig. 2. The L-116 methylation of CaM is associated with the protection of adenosine triphosphate (ATP)-ubiquitin-dependent proteolysis, thereby influencing the intracellular levels of CaM (50). The methylation state of CaM can influence the activity of target proteins in diverse ways. Previous research further corroborates that the activities of glutamate decarboxylase (GAD) and myosin light chain kinase in plants were unaffected by CaM methylation (51, 52). However, the activation of NAD kinase was negatively impacted (53, 54). Roberts and colleagues created two transgenic tobacco plants overexpressing synthetic foreign CaM (VU-1 and VU-3) using the cauliflower mosaic virus 35S promoter. The purpose was to investigate the impact of CaM methylation on NADK activity (55). VU-1 CaM contains a lysine residue that has been methylated at position 115. In contrast, VU-3 CaM has an arginine instead of lysine at position 115, which cannot undergo trimethylation. However, the rest of the amino acid sequence in VU-3 CaM is the same as in VU-1 CaM. Their findings suggested that VU-3 CaM (Lys to Arg115) exhibits equivalent CaM activity but demonstrates increased activation of NADK compared to VU-1 CaM under laboratory conditions. The growth and development of these VU-3 overexpressing transgenic plants were hindered because of the excessive activation of a CaM-modulated NAD kinase, resulting in an increase in levels of NADPH and ROS (54). In addition, several other investigations have demonstrated that the methylation of 115-Lys residue plays a crucial role in safeguarding CaMs against ubiquitination and destruction through the ubiquitin-dependent route in living organisms (56). These findings also explained the causes of dysplasia in the line expressing the VU-3 CaM. It was found that reduced methylation of CaM can disrupt the sequence of events involved in DNA replication or chromosomal partitioning during meiosis (57). Collectively, these findings not only demonstrated the responsiveness of plant NADKs to methylated CaMs but also established a precedent for the functional impact of CaM methylation.

The methylation influences the conformational dynamics of CaM when it binds to Ca^{2+} (58). In their research, they have experimentally shown the presence of radiolabelled methylated lysyl residues in BtCaM (bovine CaM) after incubation with [^{3}H-methyl] AdoMet and RnCaM KMT (from *Rattus norvegicus*). However, the role of conserved CaM trimethylation remains poorly understood and no studies have been done to verify the same in plants. Several studies have indicated that most CaMs obtained from plant tissues are primarily methylated after translation at the 116-lysine position. This methylation state has a considerable impact on their capacity to activate plant NADKs (53, 59). Methylated CaM in *Arabidopsis thaliana* exhibits strong binding with developmental and stress-related proteins such as GLP, Xyl proteins associated with cell wall formation, metabolites, glycoproteins and transcription or RNA processing regulatory proteins like CP28A (59). In tobacco overexpression of VU-3 CaM which is incapable of methylation revealed reduced seed production and pollen viability in those plants which reveals the importance of CaM methylation in the proper growth and development of plants (55). In earlier study related to the study of promoter of *OsCaM KMT* and *AtCaM KMT* revealed strong expression of *CaM KMT* promoter in the pollen of the flower (59, 60). This guarantees further investigation in both plant and animal systems.

Other post-translational changes that have significant impacts on CaM activity in plants include ubiquitination, phosphorylation, acetylation and proteasome-mediated destruction. These changes can affect how quickly CaM turns over, how stable it is, where it is in the cell and how well it binds to other proteins (61). The process of ubiquitination might cause CaM to be broken down by the proteasome, which would change the length of Ca^{2+} signalling. Phosphorylation and acetylation could also change how well CaM binds to certain CaM-binding proteins. These changes, along with the highly conserved EF-hand motifs that change shape when Ca^{2+} binds, make a multilayered regulatory system that ensures that CaM-mediated signalling networks are both specialised and flexible. A structured comprehension of these mechanisms not only elucidates CaM's function as a universal Ca^{2+} sensor but also emphasises the dynamic control by post-translational changes that incorporate environmental and developmental signals into plant cellular responses.

CaM KMT mediated regulations in plants

The expression of the CaM KMT gene is selectively regulated by phytohormones and abiotic stressors. In contrast to cytokinin (kinetin), which decreased the activity of CaM KMT, the expression of this gene was shown to be upregulated in response to auxin, salt, cold and heat stress, suggesting its involvement in hormone and stress signaling pathways (59). In another study quantitative real-time PCR (qRT-PCR) analysis revealed upregulation of *OsCaM KMT* and *OsCaM1* gene expression in response to salt stress in rice plant (60). Previous results found that when *CaM KMT* was overexpressed in *Arabidopsis*, it led to hypermethylation and a decrease in root length (59). Conversely, when *CaM KMT* was suppressed, it resulted in hypomethylation and an increase in root length. In addition, the CaM lines with reduced methylation levels also showed increased resistance to abscisic acid (ABA), cold and salt stress. This indicates that the methylated form of CaM may have a specialized interaction with effector proteins involved in several stress signaling pathways. Additionally, the

findings were corroborated by the discoveries that methylation of CaM exhibited a notably greater affinity for certain proteins, including germin-like proteins (GLP9 and GLP10), cytochrome P450 20A1 (CP20A) and N-xylose isomerase, as compared to unmethylated CaM (59). This indicates that these binding partners may be responsible for the differing responses to the methylation or unmethylated forms of CaM. Calcium/CaM improves the capacity to modulate cellular responses to diverse stimuli by altering its intracellular localisation following post-translational modification. This phenomenon has been demonstrated in the case of CaM53 in *Petunia hybrida* (62). Table 1 depicts some examples of transgenic crops engineered to characterize the role of *CaM KMT* and *CaM* in crop improvement.

Another study revealed the role of *CaM KMT* in metal stress (63). They have prepared T-DNA insertion mutant lines (*camkmt1*) in *Arabidopsis thaliana*. The resistance to Cd of the *camkmt1* knockout line was assessed by root growth assays and seedling biomass measurements using a range of doses of the hazardous metal (ranging from 5 to 20 µM). The enhanced tolerance of *camkmt1* was only significant for inhibiting root elongation and this effect was observed only at the highest concentration of Cd. The inhibitory effect of Cd on biomass was significantly less pronounced for *camkmt1* compared to the wild type at Cd concentrations of 10 and 20 µM. CaMKMT is responsible for the methylation of the primary calcium (Ca) sensor CaM (59) and Ca is known to reduce the harmful effects of Cd (64, 65). The tolerance of camkmt1 was assessed by subjecting it to a constant concentration of Cd (20 µM) and varying amounts of Ca (0.5, 1 and 1.5 mM). The growth of seedlings was not affected by changes in Ca availability in the absence of Cd. The suppression of root growth and the decrease in seedling size caused by Cd were shown to be inversely related to the concentration of Ca in the growth medium. Furthermore, the *camkmt1* line exhibited considerably higher tolerance to Cd compared to the wild type across all tested Ca concentrations. These findings collectively corroborated our screening method and confirmed the identification of a mutant. *A. thaliana* plant that is resistant to Cd and has a disrupted methylation process of CaM. The absorption and translocation of Cd in *camkmt1* did not show any notable disparity when compared to Col-0. Therefore, the increased tolerance of camkmt1 to Cd was not a result of alterations in Cd accumulation, but rather a result of an enhanced ability to handle the poisonous substance. Fig. 3 represents the probable role of CaM methylation in cellular signaling. The diagram illustrates functional differences between methylated and unmethylated forms of CaM. Methylated CaM is shown to

Table 1. Example of transgenic crops engineered for characterizing role of CaM KMT and CaM in crop improvement

S. no.	Gene name	Species	Expression state	Impact	Reference
1.	*AtCaM KMT* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	T-DNA insertion mutant	Tolerant to cadmium (Cd) toxicity	63
2.	*AtCaM KMT* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Over expression	ABA stress sensitive, stunted growth under salt stress	59
3.	*AtCaM KMT* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Silencing	Hypomethylated calmodulin, less growth inhibition in salt stress	59
4.	*AtCaM KMT* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Knock out	Hypomethylated calmodulin, longer roots, ABA stress tolerance, less growth inhibition in salt stress, temperature stress tolerance	59
5.	*AtCaM1* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Over expression	positive regulator of age-dependent leaf senescence and ABA-induced ROS production	9
6.	*AtCaM1* and *AtCaM4* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Over expression	Resistance to salt stress	10
7.	*AtCaM1* and *AtCaM4* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Knock out	Sensitivity to salt stress	10
8.	*AtCaM3* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Over expression	Increased thermotolerance	24
9.	*GmCaM4* (*Glycine max*)	*Arabidopsis thaliana*	Over expression	Salt stress tolerance	76
10.	*OsCaM1-1* (*Oryza sativa*)	*Oryza sativa*	Over expression	Tolerance to salt stress	11
11.	*OsCaM1-1* (*Oryza sativa*)	*Oryza sativa*	Over expression	Tolerance to dehydration stress	12
12.	*OsCaM1-1* (*Oryza sativa*)	*Oryza sativa*	Over expression	Reduced salt-induced oxidative damage	77
13.	*GmCaM4* (*Glycine max*)	*Glycine max*	Over expression	Enhanced resistance to three plant pathogens (*Phytophthora sojae*, *Alternaria tenuissima*, *Phomopsis longicolla*) and increased tolerance to high salt conditions	35, 36, 37
14.	*AtCaM7* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Over expression	Hyperphotomorphogenic growth irrespective of light qualities, promotes light-induced gene expression	78
15.	*AtCaM7* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	Knock out	Reduced photomorphogenesis, Reduced Expression of Light-Inducible Genes	78
16.	*AtCaM2* (*Arabidopsis thaliana*)	*Arabidopsis thaliana*	T-DNA insertional mutant	Reduction in pollen germination	79
17.	*CaCaM1* (*Capsicum annuum*)	*Arabidopsis thaliana*	Over expression	Enhanced resistance to Pseudomonas syringae and Hyaloperonospora parasitica, which was accompanied by enhanced ROS	39
18.	*NtCaM13* (*Nicotiana tabacum*)	*Nicotiana tabacum*	Silencing	Increased vulnerability to harmful necrotrophic pathogens	38

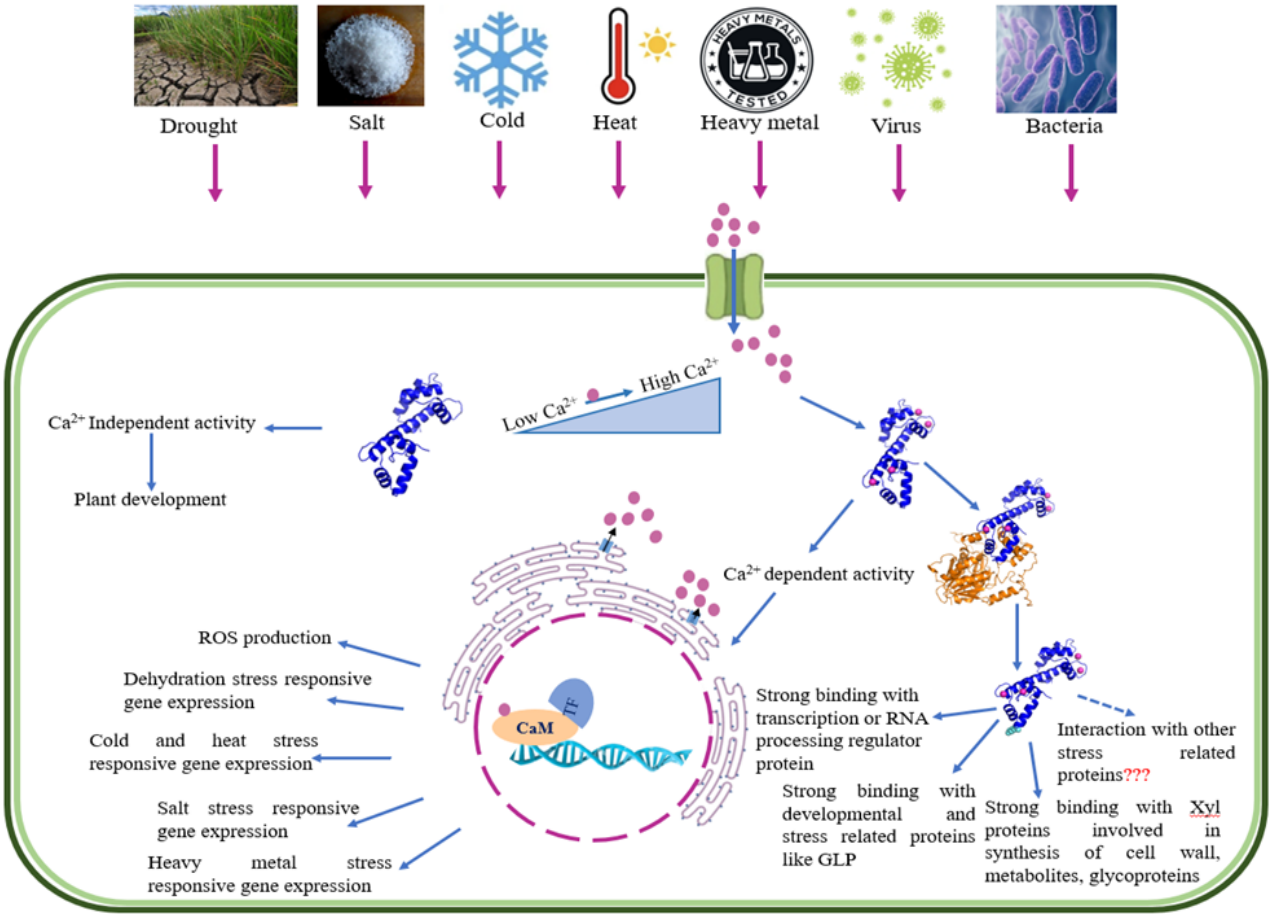

Fig. 3. Schematic diagram representing the probable role of CaM methylation in cellular signaling. The diagram illustrates functional differences between methylated and unmethylated forms of CaM. This differential modification potentially modulates CaM-dependent responses to various intracellular calcium signals (created using https://www.biorender.com/)

enhance specific protein interactions and downstream signaling pathways, whereas unmethylated CaM displays altered binding affinities and may participate in distinct regulatory mechanisms.

In addition to Ca^{2+}, divalent cations like Mg^{2+}, Mn^{2+}, Zn^{2+} and Fe^{2+} can also interact with CaM and change how it moves, albeit not as strongly as Ca^{2+} (66, 67). Plants in natural or agricultural soils are seldom subjected to a singular metal ion; instead, they are exposed to metal combinations. Exposure to these mixes might have either positive or negative effects on CaM expression and function, which would change Ca^{2+}-dependent signalling pathways in ways that are hard to anticipate. Including this part in the conversation shows how metal homeostasis and environmental pollution can have a big effect on CaM-mediated signalling. This makes the regulation of calcium sensing and downstream reactions much more complicated.

CaM KMT mediated regulations in animals

The role of CaM has been examined not just in plants but also in animals. A previous study proposed that Calcium/ CaM-dependent protein kinase II (CaMKII) of the δ subunit in the rat brain may have a role in both neuron death and the restoration of neurological function (68). CaM KMT has been isolated and characterized from lamb testicles, rat brains, unicellular eukaryotes and *Paramecium tetraurelia* (69 - 71). CaM KMT is universally expressed in many human organs and its dysregulated transcription is significantly linked to disorders like 2p21 deletion syndrome in humans (58, 72). In another study wherein patients 19 genomic region of CaM KMT was deleted along with its adjacent PREPL gene, those patients exhibited features like cleft palate and genital abnormalities (73). CaM KMT is crucial for growth, muscle strength, somatosensory development and cognitive function; any modification of the CaM KMT gene impairs CaM methylation, leading to stunted growth and muscular weakness (74). Consequently, CaM KMT serves as a crucial factor in human disorders by regulating the methylation of CaM. A recent study indicated that CaM KMT plays an anti-inflammatory role by regulating lysine trimethylation of CaM and restricting caspase-11 non-canonical inflammasome-activated inflammatory responses in macrophages (75). Their findings uncovered opportunities for the development of potential therapeutics capable of modulating CaM KMT to prevent and treat a range of inflammatory and infectious diseases.

Conclusion

The data presented in this review indicate that although work over the last few decades has provided us with knowledge of many novel roles played by CaM KMT and CaM in many abiotic and biotic stresses, further investigation is required to fully understand the significance of lysine methylation of CaM proteins in plants. First off, there is a dearth of information regarding lysine methylated proteins and further research is required to further understand the lysine methyl proteomes in plants. Secondly, the functional significance of CaM lysine methylation in plant biology will need to be explored in future studies. A comprehensive investigation of the CaM KMT protein is necessary to understand its role in methylation reactions, which are not well understood in plants. Additionally, studies are required to find out whether this

methylation of CaM is reversible or not and if reversible then also the process needs to be investigated in plants. It is important to determine whether trimethylation events on the lysine residue of CaMs may be reversed and if they have a role in dynamically regulating cellular processes. Additional research will be required to investigate the biochemical and physiological effects of methylation CaM. This includes determining the specific proteins that exclusively interact with methylated CaM, as opposed to non-methylated CaM. So far, most investigations conducted in plants have failed to reveal the significance of lysine methylation. This is likely since the impacts were too subtle to produce observable characteristics in mutants lacking methyltransferase enzymes. Future research endeavours aimed at elucidating the function of methylated CaM in stress-signaling pathways would be a significant area of study. This research would not only serve as a foundation for understanding the fundamental mechanisms involved but also offer opportunities for developing stress-resistant crop types.

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Authors' contributions

DN and JB hypothesized the idea of the research analysis and article. The required analysis and draft manuscript were prepared by DN and AC. The manuscript was reviewed and edited by JB. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest: The authors assert that they have no conflicting interests.

Ethical issues: None

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