

REVIEW

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Adenyl cyclases and cAMP in plant signaling - past and present

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Abstract

In lower eukaryotes and animals 3'-5'-cyclic adenosine monophosphate (cAMP) and adenyl cyclases (ACs), enzymes that catalyse the formation of cAMP from ATP, have long been established as key components and second messengers in many signaling pathways. In contrast, in plants, both the presence and biological role of cAMP have been a matter of ongoing debate and some controversy. Here we shall focus firstly on the discovery of cellular cAMP in plants and evidence for a role of this second messenger in plant signal transduction. Secondly, we shall review current evidence of plant ACs, analyse aspects of their domain organisations and the biological roles of candidate molecules. In addition, we shall assess different approaches based on search motifs consisting of functionally assigned amino acids in the catalytic centre of annotated and/or experimentally tested nucleotide cyclases that can contribute to the identification of novel candidate molecules with AC activity such as F-box and TIR proteins.

Is there cAMP-dependent signaling in plants?

By the mid 1970s, 3'-5'-cyclic adenosine monophosphate (cAMP) had been firmly established as an important signaling molecule and second messenger in both animals and lower eukaryotes [1-4]. It was understood that adenyl cyclases (also referred to as adenylyl or adenylylase cyclases) (ACs) catalyse the conversion of ATP to cAMP and pyrophosphate, that cAMP affects many different physiological and biochemical processes including the activity of kinases and that cAMP levels decrease in the presence of phosphodiesterases [4]. Given the growing realization of the importance of ACs and cAMP, it is not surprising that plant scientists were keen to learn if this signaling system was universal and therefore operating in plants too. As a result a controversy ensued that is perhaps best summarized by a concluding statement in a review in 1977 - "Our present knowledge, or rather ignorance, of cyclic AMP in higher plants does not permit us to indulge in speculation on its function and thus to increase the disparity between available facts and conclusions, which are based solely on the conviction that plants, with respect to cyclic AMP, should behave like animals or certain bacteria" [5]. Plant scientists were cautioned not to jump to conclusions for two reasons, firstly, the cAMP

levels in plants appeared to be low compared to that found in animals and secondly, vagaries of the assays were not conducive to firm conclusions [5]. Whilst more advanced analytical tools have since overcome the second point, the first remains [6]. Reported cAMP levels in plants are typically < 20 pmol/g fresh weight (e.g. ≤ 12 pmol/g fresh weight in rye grass endosperm cell cultures [7] and < 12 pmol/g fresh weight in *Lilium longiflorum* pistils) whereas animal values are typically > 250 pmol/g wet weight [8]. Incidentally low levels of another cyclic nucleotide, cGMP [9], were also reported in plants where e.g. specific responses to avirulent pathogens increased cytosolic cGMP from < 0.4 pmol/g fresh weight to 1 pmol/g fresh weight. It is however noteworthy that 0.5 pmol/g fresh weight of a cyclic nucleotide corresponds to a cytosolic concentration of approximately 500 pM [6], and that signaling in the picomolar range is not uncommon in plants [10,11]. Despite the low, seemingly unphysiological and certainly not animal-like levels of cAMP in plants, the notion that plants too have a functional cAMP-dependent signal system remained alive, mainly because of the fact that both cell permeant 8-Br-cAMP and stimulation of albeit unknown ACs with forskolin could elicit concentration and time-dependent biological responses such as increases in Ca^{2+} influx across the plasma membrane [12,13]. Biochemical evidence included the finding that crude alfalfa (*Medicago sativa*

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L.) root extracts showed calmodulin-dependent AC activity [14].

Arguably the most convincing data for a specific signaling role for cAMP came from whole-cell patch-clamp recordings from *Vicia faba* mesophyll protoplasts that revealed that outward K^+ current increased in a dose-dependent fashion following intracellular application of cAMP - and not AMP, cGMP or GMP - and indirect evidence indicated that this modulation occurred through a cAMP-regulated protein kinase [15]. In addition, cAMP-dependent up-regulation of a calcium-permeable conductance activated by hyperpolarization was also reported in guard cells as well as mesophyll cell of *Arabidopsis thaliana* and *Vicia faba* [16].

Cyclic nucleotide gated channels (CNGCs) from olfactory and retinal neurons are members of the S4-containing superfamily of ion channels [17,18] with their unusual stretch of hydrophobic and basic amino acids thought to serve as a transmembrane voltage sensor for channel gating [19]. The first member of this family in plants [20], AKT1, showed homology with both animal cGMP and cAMP gated channels including putative nucleotide binding sites but was described as voltage rather than cyclic nucleotide gated. Subsequently, another member of the Shaker superfamily of K^+ channels in *Arabidopsis*, KAT1, was discovered and also showed the diagnostic cluster of six putative membrane-spanning helices (S1-S6) at the amino terminus of the protein harboring the presumed voltage-sensing region containing Arg/Lys-Xaa-Xaa-Arg/Lys repeats within S4 [21]. This KAT1 was subsequently shown to be a hyperpolarization-activated K^+ channel, and importantly, that voltage dependence is also regulated by pH, ATP, and cGMP [22].

In animals systems CNGCs are non-selective cation channels with a role in sensory signal transduction, gated directly by the second messengers cAMP or cGMP. These messengers transduce stimulus-induced changes in their cytosolic concentration into altered membrane potential and cation fluxes as part of the stimulus response cascade. The first such channel characterized in plants was AtCNGC2, a cyclic-nucleotide gated, inward-rectifying K^+ channel that is blocked by mmolar concentrations of Ca^{2+} [23]. AtCNGC2 was later demonstrated to conduct K^+ and other monovalent cations but to exclude Na^+ and, that membrane transmembrane currents were directly dependent on cAMP [24]. Voltage clamp studies (two-electrode configuration) demonstrated that AtCNGC1 is also a cyclic nucleotide gated channel. In addition, cAMP has been demonstrated to induce inward rectified K^+ currents in AtCNGC1 [24]. To date there are >20 *Arabidopsis* CNGCs annotated and progress has been made in the functional characterisation of several of them, notably AtCNGC2 [25] which plays a key role in innate immunity

by facilitating Ca^{2+} currents and linking them to downstream nitric oxide production critical for the hypersensitive response (HR). Further, AtCNGC4 is permeable to both K^+ and Na^+ , is activated by both cGMP and cAMP and is induced in response to pathogen infection and some pathogen-related signals leading to the HR and eventual resistance [26]. Analyses of knock-out lines have revealed that both AtCNGC11 and AtCNGC12 are also positive mediators of resistance against an avirulent biotype of *Hyaloperonospora parasitica* [27]. This may suggest that specific cyclic nucleotide signatures generated in response to biotic [9,28] and abiotic [29] stresses act as messengers in signaling cascades that critically depend on CNGCs [30,31]. Cyclic AMP may also have an important role in abiotic stress responses and in particular responses to NaCl stress since voltage independent channels (VICs) in *Arabidopsis thaliana* roots have been reported to have open probabilities sensitive to μ molar concentrations cAMP or cGMP at the cytoplasmic side [32].

In search of ACs in higher plants

Given that cAMP plays an important role in signaling in higher plants, it is not surprising that many research groups have put considerable effort into finding ACs and in particular in *Arabidopsis thaliana*. The only annotated and experimentally confirmed AC in plants is a *Zea mays* pollen protein [33] generating cAMP which in turn is a second messenger with a role in polarized pollen tube growth. The *Arabidopsis* orthologue of this protein (At3g14460) is annotated as disease resistance protein belonging to the nucleotide-binding site-leucine-rich repeat (NBS-LRR) family used for pathogen sensing and with a role in defense responses and apoptosis [34]. NBS-LRR proteins directly bind pathogen proteins and associate with either a modified host protein or a pathogen protein leading to conformational changes in the amino-terminal and LRR domains of NBS-LRR proteins which are thought to promote the exchange of ADP for ATP by the NBS domain. It is thus conceivable that NBS-LRR downstream signaling [34] is enabled by cAMP.

Considering that cyclic nucleotides have important and diverse roles in plant signaling via cyclic nucleotide-responsive protein kinases, -binding proteins and -gated ion channels [35], it is unlikely that a single AC or GC can account for all cAMP and cGMP dependent processes in higher plants. In line with this hypothesis is the fact that a number of *Arabidopsis* molecules with different domain organizations and experimentally confirmed GC activity have recently been reported [36-38]. It is likely that the same will hold true for ACs and this leaves us with the task to identify them, a task made complicated by the fact that BLAST searches with known and/or experimentally

confirmed nucleotide cyclases from lower or higher eukaryotes do not return plausible candidate molecules with low e-values. We also note that Prosite signatures for class one and two ACs ((EYFG[SA]X(2)LWXLYK) and (YRNXW[NS]E[LIVM]RTLHFXG)) are not present in the Arabidopsis proteome even if we allow 2 mismatches.

In Arabidopsis, functionally tested GCs have been identified with a 14 amino acid long search term [36] deduced from an alignment of conserved and functionally assigned amino acids (Figure 1A) in the catalytic centre of annotated GCs [39,40] from lower and higher eukaryotes. For this reason we may expect that a similar approach might lead to the discovery of novel ACs. In the modified AC search terms the amino acid residues that confer substrate specificity (position 3 in Figure 1) will be substituted to [DE]. Consequently, the core motif within the catalytic centre consists of the functionally assigned residue that does the hydrogen bonding with the adenine (position 1), the amino acid that confers substrate specificity for ATP (position 3) and the amino acid that stabilizes the transition state from ATP to cAMP ([K,R], position 12-14). Additional diagnostic residues are the Mg²⁺/Mn²⁺ binding amino acid [E,D], usually 1 - 3 amino acids removed from C-terminal of the transition state stabilizing residue. Such a modified pattern ([RKS]X[DE]X(9,11)[KR]X(1,3)[ED]) (Figure 1B) is present in a *Zea mays* AC (AJ307886.1) which is the only experimentally tested AC in plants and it is also present in the *Sorghum bicolor* ortholog (gb|EER90437.1) and the related (2e⁻⁷⁰) Arabidopsis NBS-LRR class protein (At3g14460).

In many GCs and all experimentally confirmed GCs in Arabidopsis [36-38], the position between the assigned residue that does the hydrogen bonding (position 1) and

the amino acid that confers substrate specificity (position 3) of the core motif is [YFW] and this is also the case in the confirmed *Zea mays* AC which incidentally shares some similarity (5e⁻⁰⁵) with an annotated *Neurospora crassa* AC (XP_965280.1).

In Arabidopsis (TAIR: <http://www.arabidopsis.org>) there are currently 3 annotated but functionally unconfirmed ACs (At1g26190, At1g73980 and At2g11890) and they all do contain the motif [RKS]X[DE]X(9,11)[KR]X(1,3)[DE] (Figure 1B). The first, a phosphoribulokinase/uridine kinase family protein shows similarity (3e⁻¹⁰⁸) to an AC domain-containing protein from *Polysphondylium pallidum* PN500. This protein contains a conserved CYTH-like domain typical for the superfamily of enzymes that hydrolyze triphosphate-containing substrates and require metal cations as cofactors. The term CYTH derives from bacterial class IV adenylyl cyclases (CyaB) and thiamine triphosphatase and the domain occurs in RNA triphosphatases, membrane-associated polyphosphate polymerases, tripolyphosphatases, nucleoside triphosphatases, nucleoside tetraphosphatases and other proteins with unknown functions. Furthermore, searches initiated from the C-terminal region to the uridine kinase from *Oryza sativa* identified archaeal CyaB homologs [41]. The second candidate AC, At1g73980 has a similar domain organisation and high homology (6e⁻¹⁰⁹) to a *Dictyostelium discoideum* AX4 AC domain containing protein. The third has only some similarity to non plant proteins, one being a *Trichomonas vaginalis* G3 AC family protein (2e⁻⁰⁴). In addition, there is one putative Arabidopsis AC (At3g21465) annotated at NCBI <http://www.ncbi.nlm.nih.gov/protein/51968402>. It does contain the core motif, but has no annotated domains or

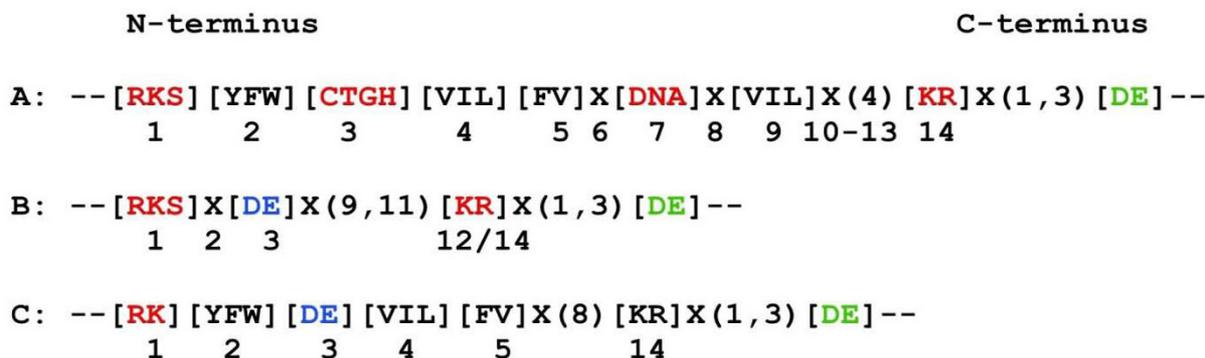


Figure 1 Catalytic centre motifs of nucleotide cyclases. (A) Centre motif of experimentally tested GCs in plants. The residue (red) in position 1 does the hydrogen bonding with the guanine, the amino acid in position 3 confers substrate specificity and the residue in position 14 stabilises the transition (GTP/cGMP). The Mg²⁺/Mn²⁺-binding site is C-terminal (green). In the derived motifs (B and C) specific for ACs, position 3 (blue) has been substituted to [DE] to allow for ATP binding.

Table 1: *Arabidopsis thaliana* proteins containing the AC search motif: [RK][YFW][DE][VIL][FV]X(8)[KR]X(1,3)[DE]

ATG No.	Sequence	Annotation
At1g25240	-KWEIFEDDFCFCKDIKE-	Epsin N-terminal homology
At1g62590	-KFDVVISLGEKMQR--LE-	Pentatricopeptide (PPR) prot.
At1g68110	-KWEIFEDDYRCFDR--KD-	Epsin N-terminal homology
At2g34780	-KFEIVRARNEELKK-EME-	MATERNAL EFFECT EMBRYO ARREST 22
At3g02930	-KFEVVEAGIEAVQR--KE-	Chloroplast protein
At3g04220	-KYDVFPSFRGEDVR--KD-	TIR-NBS-LRR class
At3g18035	-KFDIFQEKVKEIVKVLKD-	Linker histone-like prot. - HNO4
At3g28223	-KWEIVSEISPACIKSGLD-	F-box protein
At4g39756	-KWDVVASSFMIERK--CE-	F-box protein

known functions and does not share any similarity with annotated and/or experimentally confirmed ACs but appears to be transcriptionally up-regulated in response to biotic stress.

While the presence of the core motif may prove useful as supporting criterion for the identification of candidate ACs, it is not stringent enough to identify candidate ACs *ab initio*. In order to achieve this, I propose to use a previously identified 14 amino acid long GC catalytic centre search motif modified for specificity for ATP rather than GTP binding and with the C-terminal metal binding residue ([RK][YFW][DE][VIL][FV]X(8)[KR]X(1,3)[DE]) (Figure 1C). This motif retrieves 9 candidate *Arabidopsis* ACs (Table 1) including 2 F-box proteins (At3g28223 and At4g39756) and a toll interleukin receptor nucleotide-binding site leucine rich repeat protein (TIR-NBS-LRR; At3g04220). In the former, the F-box domains (cyclin like; IPR001810) have a role in protein-protein interactions and have also been associated with cellular functions such as signal transduction and the regulation of the cell cycle that in turn is linked to both auxin responses and changes in cellular cAMP content [42-44]. Given this association one might be tempted to speculate that *axi*, an auxin independence conferring gene could encode an AC, particularly since the *Arabidopsis axi1* protein does contain the AC core motif as well as the C-terminal metal binding residue.

With regards to At3g04220, we note that LRR proteins with AC domains have been reported [45]. Further, the *Zea mays* AC [33] is structurally similar to plant TIR-NBS-LRR type disease resistance proteins (e.g. ADB66335.1, *Populus trichocarpa* 4e⁻⁷⁶) and At3g04220 also contains a P-loop Ntase signature which also occurs in signal transduction ATPases with numerous domains (STAND) that in turn include ACs [46].

Conclusion and outlook

Given that our understanding of the structural features that enable nucleotide cyclase activity in higher plants is

growing, we can expect significant progress in the discovery and experimental confirmation of novel ACs in higher plants in the near future. Consequently, this will afford a better understanding of the role of cAMP as second messenger in plant development, responses to environmental stimuli and/or hormones. In addition, we are likely to see cAMP-dependent transcriptomes and (phospho-)proteomes, that, together with studies in mutants, will afford new and fundamental insights into plant signaling.

Competing interests

The author declares that they have no competing interests.

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