



REVIEW PAPER

# Interactions between cytokinin signalling and abiotic stress responses

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Received 22 December 2014; Revised 9 March 2015; Accepted 16 March 2015

## Abstract

Plants have evolved elaborate mechanisms for sensing and responding to sub-optimal environmental conditions. Abiotic stresses caused by these conditions trigger a wide range of local and long-distance signals which must be coordinated and integrated into whole-plant processes, such as development, in order for the plant to respond properly and survive. Several hormones function as key regulators of stress tolerance, connecting local stimuli to systemic responses. Cytokinin is a hormone well known for its role in numerous aspects of growth and development, although abundant evidence also indicates that cytokinin functions in stress responses as well. At present, a full understanding of the effects of cytokinin on plant resistance to stress is lacking, possibly as a result of the complex interactions between cytokinin and stress signalling. Current knowledge of the physiological relationship between cytokinin and abiotic stress, based on measurements of cytokinin levels under stress conditions and the effects of cytokinin treatment on stress tolerance, has been examined here. A pattern of transcriptional regulation of stress-related genes by cytokinin in different plant species has also been identified. In addition, research regarding the role of specific cytokinin signalling components in a variety of stress responses is presented. We discuss what this body of research collectively implies with regard to cross-talk between cytokinin and abiotic stress tolerance.

**Key words:** Abiotic stress, cytokinin, hormones, signal transduction, stress tolerance, transcription factor.

## Introduction

Cytokinin is a plant hormone that regulates a wide array of processes crucial to plant development (Werner and Schmulling, 2009; Kieber and Schaller, 2014). Cytokinin was first identified as a potent inducer of cell division in tissue culture and is now known to be a key regulator of the cell cycle (Miller *et al.*, 1955, 1956; Schaller *et al.*, 2014). Along with auxin, cytokinin plays an important role in regulating cell divisions and the maintenance of stem cells in apical meristems of both shoots (Gordon *et al.*, 2009; Zhao *et al.*, 2010; Su *et al.*, 2011) and roots (Dello Ioio *et al.*, 2008; Zhang *et al.*, 2013). Functional roles of cytokinin in growth and development at the tissue and organ level include: inhibition of lateral root initiation (Laplaze *et al.*, 2007; Bielach *et al.*, 2012), differentiation of phloem and metaxylem in roots (Mähönen *et al.*, 2000; Bishopp *et al.*, 2011), regulation of cell division

and photomorphogenic differentiation in expanding leaves (Chory *et al.*, 1994; Chiang *et al.*, 2012; Efroni *et al.*, 2013) and inhibition of leaf senescence (Gan and Amasino, 1996; Zwack and Rashotte, 2013). By contrast, interactions between cytokinin signalling, environmental stimuli, and stress have only more recently begun to be well characterized (Argueso *et al.*, 2009; Ha *et al.*, 2012; O'Brien and Benkova, 2013).

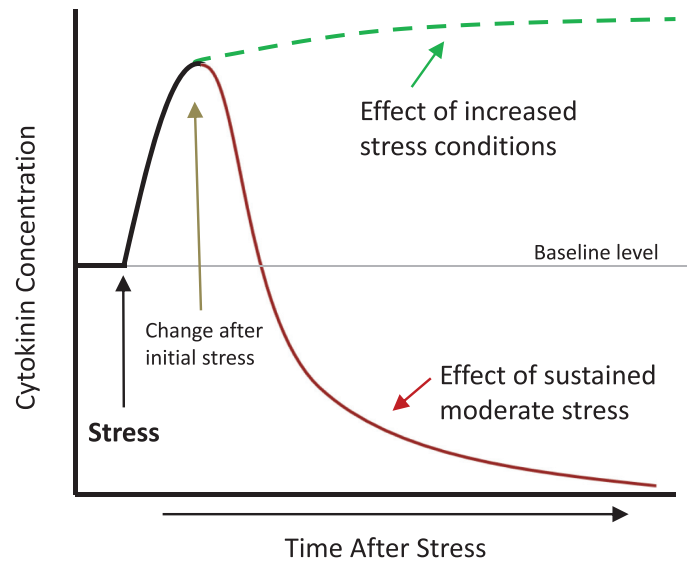
Several other plant hormones are known to function in abiotic stress responses. Abscisic acid (ABA) has long been recognized as the primary plant 'stress hormone', regulating a wide range of mechanisms leading to enhanced stress tolerance (Cutler *et al.*, 2010; Danquah *et al.*, 2014). Ethylene is also involved in the abiotic stress response, in part, by limiting growth in favour of increased stress tolerance (Morgan and Drew, 1997; Wang *et al.*, 2013). Salicylic acid and jasmonic

acid are important in stress responses as well, however, these hormones are primarily linked to biotic stress (Wasternack, 2007; An and Mou, 2011). In addition, evidence exists in support of the involvement of auxin and gibberellins in stress adaptation, which may occur indirectly through alterations in growth (Achard *et al.*, 2008; Tognetti *et al.*, 2012).

## Cytokinin plays an important and complex role in abiotic stress responses

Cytokinin is generally considered to play a negative role in plant adaptation to stress, however, this is not always clearly supported. In fact, evidence exists for cytokinin having both positive and negative effects on stress tolerance. Much of the conflicting evidence has come from physiological investigations examining endogenous cytokinin levels during and after stress treatments and/or the effects that exogenous cytokinin application has on stress tolerance. Numerous studies, conducted in a wide range of plant taxa, have found that cytokinin concentrations decrease in response to extended stress (Itai and Vaadia, 1965; Itai *et al.*, 1973; Walker and Dumbroff, 1981; Caers *et al.*, 1985; Hubick *et al.*, 1986; Hansen and Dörffling, 2003; Kudoyarova *et al.*, 2007; Albacete *et al.*, 2008; Ghanem *et al.*, 2008). By contrast, other investigations have reported both short-term and sustained increases in cytokinin levels, particularly in response to severe stress (Walker and Dumbroff, 1981; Hansen and Dörffling, 2003; Pospisilova *et al.*, 2005; Alvarez *et al.*, 2008). The measurement of cytokinin in xylem sap of stress-treated plants has indicated that cytokinin long-distance transport is reduced in some species under certain conditions, but the physiological relevance of these findings has been questioned (Burrows and Carr, 1969; Bano *et al.*, 1994; Hare *et al.*, 1997). Expression analyses of *Arabidopsis* cytokinin biosynthesis (*IPT*) and catabolism (*CKX*) genes following NaCl treatment showed that *IPT5* and *IPT7* are up-regulated for 1–2h before returning to pretreatment levels. Conversely, *CKX1*, *CKX3*, and *CKX6* are repressed after 1h followed by a gradual increase with elevated levels sustained for 5–10+ h (Nishiyama *et al.*, 2011). Taken together, analyses of cytokinin levels during the stress response could be interpreted as indicating that cytokinin concentrations first undergo a transient increase upon exposure to stress followed by either an overall decrease under sustained moderate stress or the maintenance of initially increased higher levels when challenged with more severe conditions (Fig. 1).

The effects of an exogenous cytokinin application towards regulating stress tolerance have also been examined using a variety of hormone-treatment strategies. Bean plants treated with cytokinin by foliar spray were more susceptible to salt treatment than control plants (Kirkham *et al.*, 1974). However, wheat seedlings grown on cytokinin-supplemented media and sprouted potato tubers pretreated with cytokinin demonstrated improved salt tolerance (Naqvi *et al.*, 1982; Abdullah and Ahmad, 1990). Pospisilova and Batkova (2004) found irrigation with cytokinin prior to drought increased the tolerance of bean plants, but had no effect and a negative effect



**Fig. 1.** Graphical representation of possible effects of stress on cytokinin content. Studies measuring cytokinin concentrations and expression of cytokinin metabolism genes during and after various stress stimuli suggest that, as a general stress response, cytokinin production/accumulation is rapidly elevated. This initial induction is usually transient (<3h), but may be sustained under certain conditions including severe stress.

on tolerance in maize and sugar beet, respectively. Cytokinin aided the recovery of leaf photosynthetic performance when applied following heat shock in maize and tobacco; however, cytokinin pretreatment exacerbated the negative effects of the stress (Itai *et al.*, 1978; Caers *et al.*, 1985). *Arabidopsis* plants grown on media supplemented with cytokinin had a higher survival rate than non-supplemented plants when exposed to freezing or dehydrating conditions (Jeon *et al.*, 2010; Kang *et al.*, 2012). While the plants did survive in these studies, the exogenous cytokinin resulted in overall inhibited growth. Together, these studies indicate that multiple factors influence how cytokinin treatment affects stress signalling and that the spatial, temporal, and developmental context may be important factors in the downstream stress response.

More recently a novel approach has been taken to examine the effects of increasing cytokinin levels in relation to stress tolerance. The isopentenyl transferase (*IPT*) gene from *Agrobacterium tumefaciens*, which catalyses the rate-limiting step of cytokinin biosynthesis, was inserted into the genome of tobacco plants under the regulation of a stress-inducible promoter. The resulting transgenic plants increase cytokinin levels specifically in response to stress and have enhanced drought tolerance (Rivero *et al.*, 2007). Subsequent work using this same stress-induced cytokinin circuit has replicated these findings in transgenic rice and peanut plants (Peleg *et al.*, 2011; Qin *et al.*, 2011). In apparent contrast to these findings, *Arabidopsis ipt* mutants, which have reduced cytokinin levels, are also more drought resistant compared with the wild type (WT) (Nishiyama *et al.*, 2011). Decreased cytokinin levels achieved by over-production of the cytokinin-degrading enzyme cytokinin oxidase (*CKX*) in either a constitutive or root-specific manner, also has a positive effect on drought-stress tolerance (Werner *et al.*, 2010; Nishiyama *et al.*, 2011; Mackova *et al.*, 2013). Importantly, the root-specific (*WRKY6*)

promoter used in this study is repressed in response to stress so the over-production of CKX does not persist under drought. Therefore the increased tolerance was attributed to the plants having enhanced root systems as a result of diminished cytokinin (which inhibits root growth) during development (Mackova *et al.*, 2013). Collectively, these experiments clearly demonstrate the potential impact of altered cytokinin metabolism on stress responses, and further emphasize the complex role it plays in such responses.

## Transcriptional regulation of stress related genes by cytokinin

Transcriptome-wide responses to cytokinin treatment have been examined many times. These have, in turn, recently been used in comprehensive meta-analyses of transcriptional responses to cytokinin (Brenner *et al.*, 2012; Bhargava *et al.*, 2013; Brenner and Schmulling, 2015). Among the processes from GO term/MapMan analyses, implicated as being regulated by cytokinin were abiotic stress responses, particularly response to oxidative stress—with an abundance of redox-associated enzyme activities (such as peroxidase and glutathione transferase) (Brenner *et al.*, 2012; Bhargava *et al.*, 2013). It was also shown that genes that are most highly responsive to cytokinin tend to be repressed in response to external stimuli including stress conditions (Brenner *et al.*, 2012).

To understand the regulation of stress-responsive genes by cytokinin better, induced and repressed genes from two different cytokinin transcriptome profiling experiments were separately examined in *Arabidopsis* for additional connections to stress (Rashotte *et al.*, 2003; Brenner *et al.*, 2005). Functional clusters of enriched GO biological process terms were generated using tools available at the DAVID bioinformatics resources website (Table 1) (Huang *et al.*, 2009a, b). For both experiments, the most highly enriched cluster of induced genes included the term ‘response to hormone stimulus’ along with other similar terms. From both sets of down-regulated genes the cluster with the greatest degree of enrichment was characterized by oxidative stress-related terms. A similar analysis of individually enriched terms was also conducted with publicly

available transcriptome datasets from cytokinin-treated rice (*Oryza sativa*) and tomato (*Solanum lycopersicum*) plants to determine if comparable responses occurred in these species (Table 2) (Gupta *et al.*, 2013; Sato *et al.*, 2013; Shi *et al.*, 2013). In the datasets of both species, genes with molecular functions related to the detoxification of reactive oxygen were over-represented among induced genes. Interestingly, the same terms were enriched for the repressed genes, generally at a higher threshold of significance. Tomato and rice genes repressed by cytokinin were also enriched with the GO terms ‘response to stress’ and ‘response to oxidative stress’, respectively. In agreement with this trend, an examination of differentially expressed *Arabidopsis* genes in cytokinin-deficient (and salt-tolerant) *ipt1,3,5,7* mutant plants revealed that genes involved in response to and breakdown of ROS were greatly over-represented among those with increased expression relative to the WT under normal conditions (Nishiyama *et al.*, 2012). This pattern of regulation suggests that cytokinin may act transcriptionally to alter responses to ROS, which are known to be produced as a result of a wide range of abiotic stress conditions.

## The cytokinin signalling pathway interacts with multiple abiotic stress responses

Identification of cytokinin receptors and subsequent characterization of the cytokinin signalling pathway began in the late 1990s; it is now known to be a modified version of the bacterial two-component signalling system (Kieber and Schaller, 2014). The two-component cytokinin signalling pathway (TCS) includes membrane-bound (primarily ER) hybrid histidine kinases (HKs) with a cytokinin-binding input domain (CHKs) (Wulfetange *et al.*, 2011). Upon binding of cytokinin, CHK dimers become auto-phosphorylated (Shi and Rashotte, 2012). A subsequent phosphorelay involves histidine phosphotransfer proteins (HPTs) that carry the signal into the nucleus where they phosphorylate the receiver domain of two types of response regulator proteins (RRs). Phosphorylation of B-type RRs (RRBs) activates these GARP domain-containing MYB-like transcription factors, which regulate the expression of cytokinin-responsive

**Table 1.** Most enriched clusters of biological process GO terms from cytokinin transcriptome datasets

Clustering and enrichment analyses performed using DAVID Bioinformatic Resources Functional Annotation Clustering at high stringency.

Dataset <sup>a</sup>	Representative term from top cluster	Genes in cluster (%)	Enrichment score
Rashotte <i>et al.</i> , 2003 Induced	Response to hormone stimulus	24	9.71
Rashotte <i>et al.</i> , 2003 Repressed	Response to oxidative stress	4.5	3.13
Brenner <i>et al.</i> , 2005 Induced	Response to hormone stimulus	13	16.57
Brenner <i>et al.</i> , 2005 Repressed	Response to oxidative stress	2.3	7.84

<sup>a</sup> All genes induced or repressed at any time-point  $\geq 1$  h were combined.

**Table 2.** Enrichment of molecular function GO terms related to alleviation of oxidative stress in rice and tomato

P-values of enrichment generated using DAVID Bioinformatic Resources for rice and Blast-2-Go software for tomato. Values not present were not below the threshold of  $P < 0.05$ .

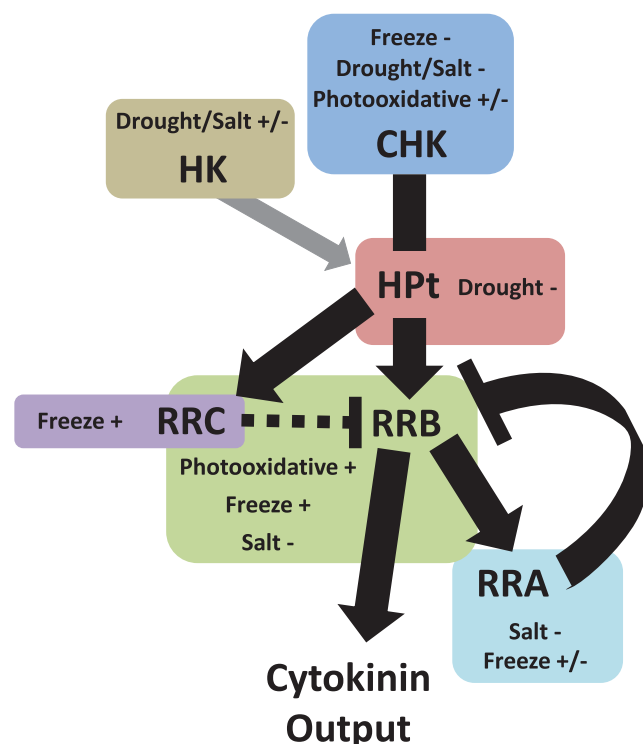
Dataset <sup>a</sup>	Antioxidant activity	Glutathione transferase activity	Peroxidase activity
Rice Induced	–	2.00E-03	–
Rice Repressed	3.20E-06	–	4.20E-07
Tomato Induced	4.80E-02	–	2.40E-02
Tomato Repressed	4.20E-02	2.30E-02	–

<sup>a</sup> All genes induced or repressed at any time-point  $\geq 1$  h in roots or shoots/leaves were combined (Gupta *et al.*, 2013; Sato *et al.*, 2013; Shi *et al.*, 2013).

genes. Among the most highly induced genes are the A-type RRs (RRAs) which are similar to RRBs but lack a DNA-binding GARP domain. As such, these proteins act as negative regulators of the cytokinin signal primarily by competing with RRBs for phosphorylation by HPTs (Gupta and Rashotte, 2012). Like the RRAs, C-type RRs (RRCs) lack a DNA-binding domain and are also believed to act as negative regulators of cytokinin signalling. The elucidation of this pathway and identification of its components, particularly in *Arabidopsis* has enabled researchers to use reverse genetic approaches to examine in greater detail specific roles of, and interactions involving, cytokinin signalling components in response to abiotic stress (summarized in Fig. 2).

### Osmotic stress: drought and salt

Loss of water potential as a result of drought or dehydration reduces transpiration and negatively impacts numerous processes including solute transport and photosynthesis (Farooq *et al.*, 2009). *Arabidopsis* possesses three CHKs (*AHK2*, *AHK3*, and *AHK4*). The expression of two of these receptors, *AHK2* and *AHK3*, is induced by drought and osmotic stress suggesting a state of heightened cytokinin sensitivity under these conditions. Plants lacking either or both of these receptors have enhanced tolerance to drought treatment as well as increased sensitivity to ABA (Tran *et al.*, 2007). This indicates that these receptors (and presumably the downstream output of the cytokinin signal) negatively impact drought tolerance. By contrast with the AHKs, expression of *Arabidopsis* HPTs (AHPs) is repressed by drought stress. *ahp2, ahp3, ahp5* triple mutants do, however, demonstrate a drought-tolerance phenotype similar to receptor mutants (Nishiyama *et al.*, 2013). Interestingly, drought induction of *Arabidopsis* A-type RRs (ARRs) *ARR5* and *ARR15* and the C-type RR *ARR22* is independent of the cytokinin receptors, implying that these downstream components of the TCS may be regulated by other additional signalling pathways (Kang *et al.*, 2012). Moreover, this same work demonstrated a positive effect of cytokinin pretreatment on drought tolerance which was enhanced in *ahk2* and *ahk3* mutants, indicating that enhancement of survival by cytokinin was not mediated by these receptors. Because loss of *AHK4* did not suppress the enhanced survival, this effect of cytokinin may have been independent of TCS signalling.



**Fig. 2.** Diagram illustrating the two-component cytokinin signalling (TCS) pathway and the relationship of its components with various abiotic stress conditions. Large solid black arrows represent known TCS interactions; dashed black blocked arrow represents predicted negative regulation; solid grey arrow represents the interaction between AHK5 and AHPs that is predicted to involve downstream components. Within the boxes associated with each class of TCS components are the abiotic stress conditions regulated by that class, the + and – indicate a positive and negative role in tolerance respectively. CHK, cytokinin receptors; HK, non-cytokinin binding histidine kinases; HPT, histidine containing phosphotransfer proteins; RRB, type-B response regulators; RRA, type-A response regulators; RRC, type-C response regulator.

Salt and drought stress have similar effects on water potential, but salinity has additional cytotoxic effects within the cell; accordingly, regulatory responses to these conditions may also be distinct (Zhu, 2002). The role of cytokinin signalling in salt stress has also been examined. As is the case for drought, *AHK2* and *AHK3* are induced by saline conditions, and single *ahk2*, *ahk3* and double *ahk2, ahk3* mutants are more tolerant of these conditions (Tran *et al.*, 2007). Consistent with this finding implying a negative regulation

of salt responses by cytokinin signalling, the B-type RR double mutant *arr1arr12* demonstrates increased salt tolerance (Mason *et al.*, 2010). However, despite greater cytokinin-sensitivity, *arr3, arr4, arr5, arr6* quadruple RRA mutants are also more salt tolerant (Mason *et al.*, 2010). This further supports the notion of RRAs interacting with other signalling systems independent of cytokinin.

In addition to the three cytokinin receptor HKs, the *Arabidopsis* genome encodes eight other HK proteins. Five of these are ethylene receptors that function independently of histidine kinase activity. The remaining three (AHK1, AHK5, and CKI1) are functional HKs, but lack cytokinin-binding capability (Schaller *et al.*, 2008). *AHK1* is induced by drought and is a positive regulator of drought tolerance, possibly acting as an osmosensor (Tran *et al.*, 2007; Wohlbach *et al.*, 2008; Kumar *et al.*, 2013). It is unknown whether this regulation is mediated through downstream TCS components. Alternatively, *AHK5*, a cytoplasmic HK, is a negative regulator of both drought and salt stress, directly interacting with AHP1, AHP2, and AHP5 (Mira-Rodado *et al.*, 2012; Pham *et al.*, 2012). Although these HK proteins are not activated by cytokinin, they may act through shared downstream components, integrating stress signalling with cytokinin responses (Fig. 2).

### Low temperature stress: cold and freezing

Cold conditions negatively impact membrane fluidity and transpiration rates leading to dysfunctions in primary metabolism. Chilling also initiates an acclimation response that prepares the plant for the more severe stress associated with freezing temperatures (Beck *et al.*, 2007). Exposure to cold, non-freezing temperatures results in transiently induced expression of the RRAs *ARR5*, 6, 7, and 15, which is dependent upon the function of the receptors *AHK2* and *AHK3*, along with *AHP2*, 3 or 5, and the RRB *ARR1* (Jeon *et al.*, 2010; Jeon and Kim, 2013). Upon extended cold treatment (6h) *EIN3*, a positive regulator of ethylene signalling, represses the expression of *ARR5*, 7, and 15 (Shi *et al.*, 2012b). This repression can be overcome by cytokinin treatment which, in addition to constitutive overexpression of *ARR5*, 7 or 15, enhances tolerance to freezing conditions (Shi *et al.*, 2012b). Plants overexpressing *ARR1* also maintain elevated levels of these RRAs during extended cold and when they are pretreated with cytokinin become more freeze-tolerant than WT controls (Jeon and Kim, 2013). These findings indicate that a subset of RRAs positively regulate resistance to freezing temperatures (Fig. 2).

By contrast, *arr5*, *arr6*, and *arr7* mutants are reported to have enhanced freeze tolerance and the overexpression of *ARR7* results in greater susceptibility to freezing (Jeon *et al.*, 2010). In addition, inducible overexpression of the type-C RR *ARR22*, represses the expression of several RRAs, including *ARR5*, 6, and 7; and results in increased resistance to cold (and drought) stress (Kang *et al.*, 2013). These conflicting results make it difficult to determine the precise role of cytokinin signalling in cold-acclimation, yet it seems clear that proper expression, particularly of a subset of RRAs, is crucial for optimal tolerance of freezing conditions.

### Photooxidative stress

Emerging evidence has implicated cytokinin signalling in additional abiotic stresses related to photosynthetic dysfunction leading to the production of reactive oxygen species (ROS) (Fig. 2). Loss of *AHK2* and *AHK3* resulted in greater photooxidative stress tolerance as indicated by decreased proline accumulation, lipid peroxidation, and chlorophyll loss. This was interpreted as an indication that these receptors negatively regulate tolerance under such conditions (Danilova *et al.*, 2014). A recent report that *ahk2,3* and *arr1,12* double mutants were hypersensitive to high-light stress, indicates that cytokinin signalling may play a positive role in this response, again illustrating the complex nature of interaction between cytokinin and abiotic stress responses (Cortleven *et al.*, 2014).

It should be noted that clear connections also exist between cytokinin signalling and biotic stress. These important interactions have been reviewed elsewhere and are outside the scope of this review (Argueso *et al.*, 2009; O'Brien and Benkova, 2013).

### Cross-talk between ABA and cytokinin signaling

Some of the changes in stress tolerance associated with cytokinin signalling and the metabolism mutants described above are also accompanied by alterations in ABA sensitivity (Tran *et al.*, 2007; Jeon *et al.*, 2010; Nishiyama *et al.*, 2011). In addition, cytokinin-deficient plants have decreased levels of ABA, due to a repression of ABA biosynthesis (Nishiyama *et al.*, 2011; Mackova *et al.*, 2013). Treatment of *Arabidopsis* plants with ABA has been shown to repress the expression of the type-A RRs *ARR6* and *ARR9*, an effect greatly diminished in *ahk2,ahk4* and *ahk3,ahk4* double mutants. This implies that this RRA repression occurs, at least in part, by direct interaction with the TCS pathway (Yang *et al.*, 2014).

Direct interactions between the cytokinin and ABA signalling pathways have been described in the regulation of other (non-stress) processes. For example, during seed germination *ARR4*, 5, and 6 proteins interact with and inhibit the function of the transcription factor *ABI5*, a positive regulator of ABA signalling (Wang *et al.*, 2011). Another component of the ABA signalling pathway, *ABI4*, which functions in a manner similar to *ABI5*, induces the expression of *ARR5* in lateral root formation (Shkolnik-Inbar and Bar-Zvi, 2010). In addition, cytokinin signalling enhances cotyledon greening by promoting degradation of *ABI5* in a manner dependent upon several different parts of the TCS: *AHK4*, *AHP2*, *AHP3*, *AHP5*, and *ARR12* (Guan *et al.*, 2014). Although such interactions have not been demonstrated in the regulation of the abiotic stress response, these findings support the feasibility of similar mechanisms of cross-talk.

Recently, a very different cytokinin-ABA interaction, not involving the TCS, was reported. ABA-mediated stomatal closure in response to drought involves the production of nitric oxide (NO). Cytokinin inhibits this process through direct interaction with and reduction of the NO molecule,

acting as a scavenger of this signalling molecule (Liu *et al.*, 2013a). Thus, in at least this case, cytokinin itself is directly involved in modulating the ABA response.

## Cytokinin Response Factors: integrators of cytokinin and abiotic stress responses

Cytokinin Response Factors or CRFs comprise a small monophyletic group of AP2/ERF transcription factors that function as a side branch of the TCS pathway (Rashotte *et al.*, 2006). CRF proteins interact with TCS components, primarily HPTs and, to a lesser extent, type-A and type-B RRs, however, the function of these interactions is unclear (Cutcliffe *et al.*, 2011). An evolutionarily conserved subset of CRFs are transcriptionally induced by cytokinin, placing them downstream of the TCS pathway, yet CRFs themselves regulate transcriptional responses to cytokinin in concert with the RRBs (Rashotte *et al.*, 2006; Shi *et al.*, 2012a; Zwack *et al.*, 2012). CRFs have been functionally linked to classical cytokinin-regulated processes (Rashotte *et al.*, 2006; Okazaki *et al.*, 2009; Zwack and Rashotte, 2013), and a large amount of correlative (expression-based) evidence suggest roles in stress response but, to date, few such roles have been demonstrated experimentally.

Analysis of microarray data indicates that *Arabidopsis* CRFs are responsive to various abiotic stresses (Argueso *et al.*, 2009). Similar expression patterns have been shown for CRFs from tomato (*Solanum lycopersicum*) and Chinese cabbage (*Brassica rapa*) (Shi *et al.*, 2012a, 2014; Liu *et al.*, 2013b; Gupta and Rashotte, 2014). Additional studies have provided more detailed information about the regulation of CRFs in response to specific abiotic stresses.

Lee *et al.* (2005) demonstrated that *CRF3* is induced at low temperatures and that this regulation is mediated by the cold responsive transcription factor ICE1. In *Arabidopsis*, *CRF4* has the greatest sequence similarity to *CRF3*. A separate study using reporter genes and quantitative PCR (qPCR) showed that this gene is highly induced by cold as well. A role in cold-acclimation was demonstrated in this instance as constitutive overexpression of *CRF4* enhanced freeze tolerance in non-acclimated plants (Compton, 2012).

The tobacco CRF referred to as Tobacco stress-induced gene 1 (*Tsi1*) was originally identified in a screen for salt-inducible transcripts. Overexpression of the *Tsi1* protein was found to confer greater tolerance, not only to salt but also to pathogen attack which was taken to suggest that it was a positive regulator of two distinct responses (Park *et al.*, 2001). Expression of the tomato orthologue of *Tsi1* (*SICRF1*) is also induced by salt but a similar functional role in salt stress has not been demonstrated (Shi *et al.*, 2012a).

*CRF6* is the most widely stress-regulated *Arabidopsis* CRF and is particularly responsive to oxidative stress (Zimmermann *et al.*, 2004; Inze *et al.*, 2012; Zwack *et al.*, 2013; Ramireddy *et al.*, 2014). In agreement with this trend, qPCR and promoter:GUS experiments have demonstrated *CRF6* induction by salt, heat shock, and H<sub>2</sub>O<sub>2</sub> (Zwack *et al.*, 2013). This expression pattern may be evolutionarily conserved as qPCR

analyses showed that the tomato *CRF6* orthologue (*SICRF5*) is also induced by heat and H<sub>2</sub>O<sub>2</sub> as well as drought (Gupta and Rashotte, 2014). A recent study identified *Arabidopsis CRF6* as a member of the mitochondrial dysfunction (MD) stimulon, a set of 24 genes which are highly responsive to MD leading to the production of ROS (De Clercq *et al.*, 2013). This retrograde signal is mediated largely by the transcription factors ANAC013 and ANAC017 which directly target *CRF6* and the closely related *CRF5* (Ng *et al.*, 2013). This finding suggests that *CRF5* and *CRF6* along with their downstream targets may play a role in the response to stress-induced mitochondrial dysfunction, yet this remains to be experimentally tested.

## Conclusions

Although the majority of cytokinin research has focused primarily on the regulation of developmental processes, the involvement of this hormone in stress responses has long been the subject of investigation. However, much about the relationship between cytokinin and stress tolerance and/or susceptibility remains unclear. Examinations of endogenous cytokinin levels under various conditions have suggested that cytokinin metabolism is highly regulated during the response to abiotic stress. Collectively, the findings of these hormone quantification studies seem to indicate that a transient spike of cytokinin occurs in the initial response to stress followed by a subsequent reduction in overall levels. This reduction, however, may not occur in the case of more severe stress conditions. Experiments involving the treatment of plants with exogenous cytokinin or biotechnological manipulation of endogenous levels have demonstrated both positive and negative effects on the tolerance of different stresses; therefore, generalizations about the effect of manipulating cytokinin levels with respect to overall stress tolerance are more difficult to make at this time.

Cytokinin signal transduction occurs via a multi-step His to Asp phosphorelay pathway and the signalling components have been identified in several species, but are most extensively characterized in *Arabidopsis*. The CHK receptor proteins from *Arabidopsis* (primarily AHK2 and 3) are antagonistic of drought, salt, and cold-stress tolerance; yet have a positive role in the adaptive response to high-light stress. Similarly, conflicting results have been found for type-A RRs as well. Overall, the current body of research suggests that the interactions between components of the cytokinin signalling pathway and stress responses are variable and context-specific. It is likely that many of these interactions occur as a result of cross-talk between cytokinin and ABA signalling and metabolism.

CRF proteins are emerging as potential integrators of cytokinin and stress responses. These transcription factors are (along with RRBs) co-regulators of cytokinin responses, yet little is known about the mechanisms of this co-regulation. It seems likely that CRFs are involved in the regulation of other transcriptional responses independent of RRBs. As such CRFs could serve to co-ordinate such responses along with the transcriptional output from cytokinin signalling.

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