

Conscientiousness of Mitogen Activated Protein Kinases in Acquiring Tolerance for Abiotic Stresses in Plants

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Mitogen activated protein kinase (MAPK) is a conserved signalling cascade among eukaryotes. It is usually a three component signalling cascade comprising of a MAPK kinase kinase, a MAPK kinase and finally a MAPK connected to each other by an event of phosphorylation. All these three component are multigene family in plants. MAPK gets activated upon phosphorylation and in turn regulates variety of proteins both in cytosol and nucleus. MAPK are basically very sensitive enzyme and gets activated by a myriad of stimuli both biotic and abiotic. Besides sensing the stimuli, MAPKs have their role in development, senescence and other vital processes of a plant life. In the present review the role of MAP kinase in transducing abiotic stress signal have been discussed.

Key Words: Abiotic Stress; MAPK; Signal Transduction

Introduction

All living cells sense, act in response to changes in the extracellular environment (biotic or abiotic) and communicate signals accordingly, also to their nucleus where changes in gene expression may occur. To carry out communications/signals, cells have evolved many different mechanisms during the course of evolution. This includes protein phosphorylation by specific protein kinases and de-phosphorylation by protein phosphatases. Activation and de-activation of enzymes through phosphorylation/de-phosphorylation by kinases and phosphatases are found essential for any specific signal transduction, and amplification of external stimuli (Brown *et al.*, 1997; Morris, 2001; Rodriguez *et al.*, 2010). Protein kinases comprise the principal gene families of protein phosphorylation, which is the most important regulatory mechanism known to control protein activity inside cells. The machinery for protein phosphorylation is highly conserved among all eukaryotes. By adding phosphate groups to the

substrate proteins, the protein kinases activate or deactivate enzymes required for signal transduction for the specific cellular activity. Protein kinases are essential in the perception of environmental stimuli and triggering signalling cascades that in turn direct cell division, cellular differentiation, metabolism, and stress responses. One among the most important protein kinases for activation or deactivation of the genes regulating cellular activity, are mitogen-activated protein kinases (MAPK). These protein kinases are essential for transduction of cellular signals in all eukaryotes, including yeasts, animals and plants. The MAPKs are acknowledged as signalling machinery for regulation of physiological and developmental responses such as cell growth, cell differentiation, hormone signalling, pathogen infection, wounding, drought, low temperature, high salinity etc. (Jonak *et al.*, 1999; Joshi *et al.*, 2011). The MAPK genes were first identified in 1993 as D5 kinase in pea (Stafstrom *et al.*, 1993) and as MsERK1 in alfalfa (Duerr *et al.*, 1993). Afterwards, the cDNA of MAPKs have been cloned in many plant species

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(Sinha *et al.*, 2011). The major milestones in the discovery of MAPK with special emphasis on plant MAPK have been described earlier (Morris, 2001; Rodriguez *et al.*, 2010; Sinha *et al.*, 2011; Mishra *et al.*, 2006; Opdenakker *et al.*, 2012). The present review describes role of MAPK cascades in acquiring tolerance for abiotic stresses.

Mitogen Activated Protein Kinases - Location, Structure and Functions

The MAPKs are located both in the cytoplasm and nucleus of cells and are occupied in diverse signal transduction pathways (Rodriguez *et al.*, 2010; Joshi *et al.*, 2011; Mishra *et al.*, 2006). Structurally the MAPKs are found in the form of a linear cascade of three protein kinases in a row. The three components of the cascade are (i) MAP kinase kinase kinase (MAPKK kinase or MAPKKK or MKKK or MEKK or MAP3K), (ii) MAP kinase kinase (MAPK kinase or MAPKK or MEK or MKK or MAP2K) and (iii) MAP kinase (MAPK or MPK) which are functionally interlinked and mediate sequential phosphorylation reactions. MAPKKK is an upstream activator of MAPKK. Generally, this activation occurs by the phosphorylation on two serine/threonine residues on MAPKK in a conserved S/T-X₃₋₅-S/T motif. The phosphorylated MAPKK in turn activates MAPK, the downstream component of the cascade, by phosphorylation of the threonine and tyrosine residues in TEY or TDY motif located in the activation loop (T-loop) between kinase domain VII and VIII (Joshi *et al.*, 2011; Sinha *et al.*, 2011; Opdenakker *et al.*, 2012; Cobb and Goldsmith, 1995; Chang and Karin, 2001; Jonak *et al.*, 2002; Nakagami *et al.*, 2005). The MAPK activator is indeed a dual-specificity (serine/threonine and tyrosine) protein kinase with strong specificity for MAPK. All MAPK are two lobed structures generally containing a TEY phosphorylation motif in the activation loop (TEY subtype) or a TDY motif (TDY subtype) within its active site buried at domain interface (Taj *et al.*, 2010). The formation and integrity of a specific MAPK cascade can be mediated by scaffold proteins, shared docking domains, and adaptor or anchoring proteins (Sinha *et al.*, 2011). In plants, these protein phosphorylation cascades link extracellular stimuli

to a wide range of cellular responses and phosphorylate a variety of substrates conscientiously. The substrates include transcription factors, transcription regulators, splicing factors and other protein kinases. Any signal transduction pathway starts with signal perception, followed by generation of second messengers like inositol phosphates (IP) and reactive oxygen species (ROS). These second messengers modulate intracellular Ca²⁺ levels which then initiate phosphorylation cascades controlling specific sets of stress regulated genes (Rodriguez *et al.*, 2010).

In accordance with amino acid sequences, MAPKs share highly conserved region over the entire lengths with highest similarity in the eleven domains that are necessary for the catalytic function of serine/threonine protein kinases (Ichimura *et al.*, 2002). The upstream MAPKKKs form the largest group of the MAPK components, which can be divided into two major subgroups - MEKK-type and Raf-like kinases (Opdenakker *et al.*, 2012; Rao *et al.*, 2010). The MAPKKs are the smallest group and are subdivided in four groups (A, B, C and D). Group A and C seem to be involved in various abiotic stresses (Opdenakker *et al.*, 2012; Kumar *et al.*, 2008; Kumar *et al.*, 2013). The MAPKs are also classified into four groups which are further divided into two broad groups based on amino acid motifs: (i) MAPKs containing TEY motif consisting of group A, B and C and (ii) MAPKs containing TDY motif consisting of only group D (Opdenakker *et al.*, 2012; MAPK Group, 2002; Hamel *et al.*, 2006). Among the four sub-groups, A and B have been intensively studied so far and most of the studies on the plant MAPK genes have been carried out in model plant species *Arabidopsis*, tobacco and rice. Each sub-group owns various members involved in environmental responses in signalling of biotic and abiotic stresses such as cold, drought, wound, pathogen attack etc. (Jonak *et al.*, 1996; Xiong and Yang, 2003; Jonak *et al.*, 2004).

Meticulousness of MAPK in Acquiring Tolerance for Abiotic Stresses

Though plants are always bound to face variety of environmental stresses, their survival is possible due

to their complicated defence strategies and MAPK cascade plays an important role towards this cause. To withstand these stresses plants in different climatic zones have developed specific mechanisms including changes in the composition of the major cell components as a consequence of expression of novel genes. It is well known that water availability and extreme temperatures are the most important limiting factors for development and growth of all plants. Along with drought and water availability, salinity, heat, cold, wounding, UV radiation etc. are also described as major abiotic stresses that always affect growth of the standing crop plants. However, the most adverse are drought, salinity and extreme temperature as these directly put negative impacts on crop productivity. Throughout evolution, plants have developed strategies to tolerate these environmental

stresses. Plant cells are skilled for perceiving stresses through definite sensors/receptors available in the cell membrane and transduce them down using a MAPK cascade (Fig. 1). A connection between the activation of a plant MAPK cascade and one common second messenger- H_2O_2 , has been demonstrated in *Arabidopsis* through protoplast transient expression assay (Tena *et al.*, 2001). H_2O_2 is generated by various environmental and developmental stimulants and can act as a signalling molecule that regulates development, stress tolerance and programmed cell death in plants (Taj *et al.*, 2010). Generally exposure to stress in plant cells induces production of messengers like ROS or Inositol-1,4,5-triphosphate (IP3), and modulation of intracellular calcium (Ca^{2+}) (Xiong *et al.*, 2002). Production of messengers is usually receptor mediated. Often these messengers

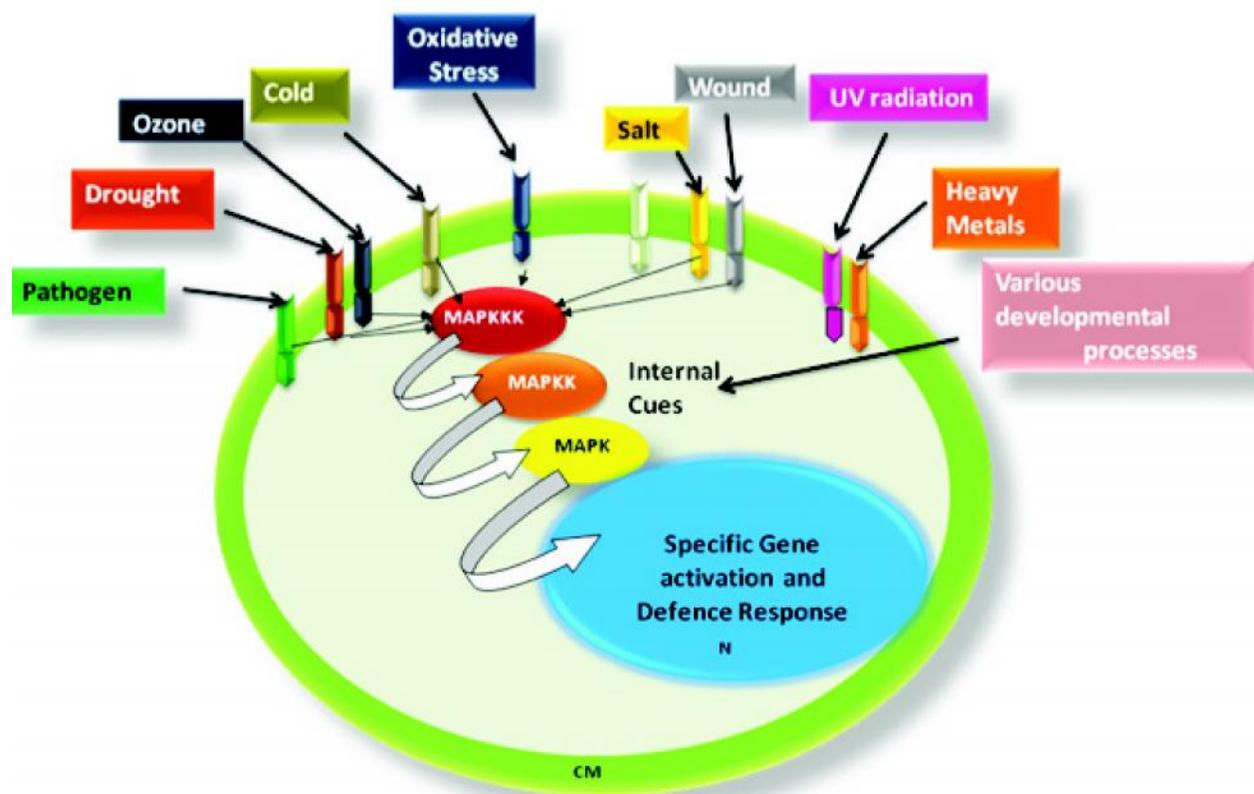


Fig. 1: An illustration of a cell showing conscientiousness of MAPK cascade for specific gene activation and defence response to withstand abiotic stresses like cold, drought, wound, salt, heavy metals, ozone and oxidative stresses. Specific signals of specific stresses are first perceived by the specific sensors present in the cell membrane (CM). Then these sensors transduce signals to the upstream component of the MAP Kinase cascade by phosphorylation of MAPKKK. The activated MAPKKK then passes signals to MAPKK by phosphorylating it on conserved serine and threonine residues. The active MAPKK consequently phosphorylates and passes signal to the downstream component of the cascade – MAPK on its conserved threonine and tyrosine residue. Later active MAPK then passes signals to nucleus (N) for specific gene activation and defence response for stress tolerance

influence each other also. Secondary messengers are capable of modulating intracellular calcium levels that habitually switch on any protein phosphorylation cascade, leading to the activation of proteins directly involved in cellular protection (Tena *et al.*, 2001). ROS and Ca²⁺ dependent signals initiate specific phosphorylation cascades (*e.g.*, MAPK, calcium dependent protein kinases-CDPK), and finally interact with the promoter regions of transcription factors (TF) and response genes.

Specific sensors sense specific stress stimuli and transmit signals to activate specific transcription factors accordingly (Fig. 1). When plant cells perceive any stress stimulus, they immediately activate signalling machinery comprising protein kinases that direct gene expression consequently to change their physiological status as a defence mechanism. According to Rodriguez and his co-workers, signal transduction networks for cold, drought and salt stress can be divided into three major signalling types: (i) osmotic/oxidative stress signalling, (ii) Ca²⁺ dependent signalling, and (iii) Ca²⁺ dependent salt overlay sensitive (SOS) signalling (Rodriguez *et al.*, 2010).

Osmotic/oxidative stress signalling is a phosphoprotein module for abiotic stress signalling in plants. Various abiotic stresses initiate generation of ROS scavenging enzymes and antioxidant compounds as well as osmolytes that inhibit photosynthesis and cause extensive cellular damage. This phenomenon is called oxidative stress and is identified as one of the major causes of plant damage as a result of environmental stresses (Rodriguez *et al.*, 2010; Sunkar *et al.*, 2003). Plants have developed many antioxidant strategies to scavenge these toxic compounds. Enhancement of antioxidant defence in plants can thus increase tolerance to different stress factor antioxidants (ROS scavengers) and include enzymes like catalase, superoxide dismutase (SOD), ascorbate peroxidase (APX) and glutathione reductase as well as non-enzyme molecules such as ascorbate, glutathione, carotenoids and anthocyanins (Xiong *et al.*, 2002). The osmotic/oxidative stress signalling involves MAPK pathway, which is activated by protein tyrosine kinases, G-protein

coupled receptors and two-component histidine kinases in response to osmotic stress and is responsible for increased production of osmolytes. These osmolytes are important for osmotic adjustment (Rodriguez *et al.*, 2010; Taj *et al.*, 2010). Ca²⁺ dependent signalling is well known in various intracellular signalling processes. Cold, drought and salinity have been shown to induce transient Ca²⁺ influx into the cell cytoplasm. Calcium dependent protein kinases (CDPKs) are implicated as important sensors of calcium influx in plants. Ca²⁺ dependent signalling lead to the activation of late embryogenesis abundant (LEA)-type genes, and involves in the production of stress-responsive proteins. Ca²⁺ dependent salt overlay sensitive (SOS) signalling regulates ion homeostasis under salt stress and involves the SOS pathway (Rodriguez *et al.*, 2010; Taj *et al.*, 2010).

There is a diversity of stress perception machinery and signalling pathway mechanisms in plant cells, some of which are specific while others cross-talk at various steps. These perception machineries work under control of MAPKs mostly to deal with environmental stress stimuli such as cold, freezing, heat, drought, ozone, UV light, salinity, osmotic shock, and mechanical wounding, though each stress stimulus induces kinase activity in a distinct manner (Sinha *et al.*, 2011). It is well known that MAPK cascades of plants are involved in responses to various stresses, hormonal responses, and other cellular processes (Sinha *et al.*, 2011; Tena *et al.*, 2001; Jonak *et al.*, 1994; Hirt, 2000). In the plants exposed to different abiotic stresses *e.g.* touch, cold, salinity, UV irradiation, ozone and oxidative stress, specific-induction of MAPK genes and increased MAPK activity have been observed (Sinha *et al.*, 2011). Cold, drought and salt stresses all stimulate the accumulation of osmolytes and antioxidants (Hasegawa *et al.*, 2000). The outcome of MAPK activation depends on the duration of its activation. The length of time that a MAPK remains active depends on the upstream specific regulation mechanisms, of which scaffolding (co-localization) and attenuation through phosphatases are best known (Sinha *et al.*, 2011). Different MAPKs are activated by salt stress at different times after the onset of stress

Table 1: Induction of specific MAP Kinases under various abiotic stresses in three model plants

Abiotic stress	Involvement/activation of MAPK component in		
	<i>Arabidopsis thaliana</i> (At)	<i>Nicotiana tabacum</i> (Nt)	<i>Oryza sativa</i> (Os)
Cold	<i>At</i> MEKKK1	<i>Nt</i> NPK1	<i>Os</i> MEK1
	<i>At</i> MKK2		<i>Os</i> MAPKK4
	<i>At</i> MPK4		<i>Os</i> MAPKK6
	<i>At</i> MPK6		<i>Os</i> MAPKK10-2 <i>Os</i> MAPK1 <i>Os</i> MAPK4 <i>Os</i> MAPK5 <i>Os</i> WJUMK1
Drought	<i>At</i> MKK1	<i>Nt</i> NPK1	<i>Os</i> MAPKK1
	<i>At</i> MPK4		<i>Os</i> EDR1
	<i>At</i> MPK6		<i>Os</i> MAPK5 <i>Os</i> MAPK33 <i>Os</i> MSRMK2 <i>Os</i> MSRMK3
Heavy metals	<i>At</i> MEKK1		<i>Os</i> EDR1
	<i>At</i> MPK3		<i>Os</i> MSRMK2
	<i>At</i> MPK6		<i>Os</i> MSRMK3 <i>Os</i> WJUMK1 <i>Os</i> MPK2 <i>Os</i> MPK3 <i>Os</i> MPK4 <i>Os</i> MPK6
High salt/ sugar/hyper- osmolarity/ osmotic stress	<i>At</i> MKK1	<i>Nt</i> NPK1	<i>Os</i> MAPKK1
	<i>At</i> MKK2		<i>Os</i> MAPKK4
	<i>At</i> MPK3	<i>Nt</i> SIPK	<i>Os</i> MAPKK6
	<i>At</i> MPK4		<i>Os</i> EDR1
<i>At</i> MPK6		<i>Os</i> MAPK33	
Salinity	<i>At</i> MEKKK1		<i>Os</i> EDR1 <i>Os</i> MAPK4
UV-B radia- tion/ozone	<i>At</i> MPK3	<i>Nt</i> SIPK	<i>Os</i> MSRMK2
	<i>At</i> MPK6	<i>Nt</i> MPK4	
Touch/woun- ding/mecha- nical stimu- lation	<i>At</i> MEKKK1	<i>Nt</i> MEK2	<i>Os</i> EDR1
	<i>At</i> MKK1	<i>Nt</i> SIPK	<i>Os</i> MAPK5
	<i>At</i> MPK4	<i>Nt</i> WIPK1	<i>Os</i> MSRMK2
	<i>At</i> MPK6	<i>Nt</i> MPK4	<i>Os</i> BWMK1

and the activities of these MAPKs are activated within different time periods (Taj *et al.*, 2010). Specificity of different MAPK cascades functioning within the same cell is conferred by docking domains of scaffold proteins, which anchor different MAPK modules in one complex (Rodriguez *et al.*, 2010; Mishra *et al.*, 2006).

Using specific antibodies approach, it is possible to identify activation of specific component of the cascade. Various stress-responsive genes that play important roles in plant drought resistance have been recognized now (Xie *et al.*, 2012). Mizoguchi *et al.* 1996 have reported that MAPK3 responds to a variety of abiotic stress including drought, cold, and salinity and is sensitive to touching and mechanical stress in *Arabidopsis*. A complete MAPK signal module for cold and salt stresses has been identified in it. The cascade consists of MEKK1 as an upstream activator of MAP2K and the downstream MAPKs MPK4 and MPK6 (Teige *et al.*, 2004). MEKK1 is activated by most of the abiotic stress conditions (Mizoguchi *et al.*, 1996) and it activates downstream signalling modules MKK1, MKK2 and MPK4 (Ichimura *et al.*, 1998). Often the abiotic and biotic stress responses share similar signalling modules. For example the signalling pathway represented by MEKK1-MKK1/2-MPK4, which is reported as the backbone of pathogen-induced responses and to play an important role in mediating homeostasis of ROS, is also vital for maintaining abiotic stress tolerance (Šamajová *et al.*, 2013). Studies in *Arabidopsis* suggest that salt, drought and wounding stresses activate MKK1 (Xing *et al.*, 2007), ozone activates MPK3 and MPK6 (Ahlfors *et al.*, 2004), hypo-osmolarity activates MPK3, MPK4 and MPK6 in cell suspension and plantlets of *Arabidopsis* (Droillard *et al.*, 2004), while oxidative stress induced by exogenous H₂O₂ can activate MPK1 and MPK2 (Ortiz-Masia *et al.*, 2007). ROS act upstream of MPK3, MPK6 (Kovtun *et al.*, 2000), MPK4 (Nakagami *et al.*, 2006) and MPK7 (Do'czi *et al.*, 2007) in *Arabidopsis*. MPK3 and MPK6 together with their upstream activators MKK4 and MKK5 regulate stomatal development and patterning and are also important in ROS-induced signalling (Šamajová *et al.*, 2013; Wang *et al.*, 2007). Lee and Ellis (2007) observed that MAPK phosphatase 2 is an important positive regulator of the cellular response to ozone that can affect the activation state of MPK3 and MPK6. In tobacco, MPK4 plays an important role in ozone sensitivity and jasmonic acid (JA) signalling. Using transgenic plants, it was studied in tobacco that MPK4 plays active role in the response to wounding

and also in ozone tolerance by regulating stomatal closure (Gomi *et al.*, 2005). MAPK pathways and stress tolerance in response to various environmental stimuli have also been widely studied in rice (Šamajová *et al.*, 2013; Rao *et al.*, 2011; Raina *et al.*, 2012; Raina *et al.*, 2013). Prolonged incubations at low temperatures (12°C) may lead to male sterility and various growth arrest phenotypes in rice with involvement of several MAPKs in the process (Wen *et al.*, 2002). Similarly, OsWJUMK1 (Agrawal *et al.*, 2003) and OsMAPK4 (Fu *et al.*, 2002) are specifically responsive to cold stress. Whereas, OsMSRMK2 and OsMSRMK3 are described as multiple stress responsive kinases and found to be induced by a plethora of abiotic stresses like wounding, salinity, drought, heavy metals, fungal elicitors or UV radiation (Šamajová *et al.*, 2013; Agrawal *et al.*, 2003). OsMAPK5 is another example of MAPK, which has multiple roles in both biotic and abiotic stress responses (Xiong and Yang, 2003). Heavy metals like cadmium and copper induce MAPK3 and MPK6 in rice (Yeh *et al.*, 2007). In rice, it was shown that Arsenic activates OsMPK3 and OsMPK4 (Rao *et al.*, 2011). The transcripts of many OsMPKs are induced by abiotic and biotic stresses and OsMPK3 positively regulates drought, salt and cold stress tolerances in rice (Xie *et al.*, 2012). Induction of OsMAPK33 by drought stress has been described by Lee *et al.* (2011). Recently a novel nuclear protein kinase - Drought-sensitive mutant 1 (DSM1) has been identified with sequence similarity to Raf-like MAP3Ks. This protein kinase plays critical roles in drought and oxidative stress resistance in rice (Ning *et al.*, 2010). Likewise, SIMKK-SIMK in alfalfa and NtMEK2 (MAP2K)-SIPK/WIPK (SA-Induced Protein Kinase/Wounding-Induced Protein Kinase) in tobacco are reported to be involved in osmotic stress (Kiegerl *et al.*, 2000; Yang *et al.*, 2001). Activation of four distinct MAPKs such as SIMK, MMK2, MMK3 and SAMK was reported later on exposure of *Medicago sativa* seedlings to the excess of copper or cadmium ions (Jonak *et al.*, 2004). Reports also describe the possibility that different MAPKs may interact with specific MAPKKs and multiple MAPK cascades may be induced by the same

signal and this has been implicated as cross-talk between components of the MAPK cascades. The reports available so far reveal that several stress-induced MAPKs and their upstream activators such as MAP2Ks and MAP3Ks are actively engaged in the regulation of diverse plant developmental processes and stress tolerance. Table 1 summarizes different model plant MAPKs being activated under various abiotic stimuli.

Conclusion

MAPK signal transduction pathways pass on information of the extracellular environment to nucleus of the cell where gene expression may occur according to the signal specificity. Among all eukaryotes, MAPK signalling pathways are highly conserved modules that are composed of a number of protein kinases that phosphorylate and thereby change the activity of their respective target proteins. Specific cascades are induced by different biotic and abiotic stress stimuli such as pathogen infections, heavy metal, wounding, high and low temperatures, high salinity, UV radiation, ozone, reactive oxygen species, drought and high or low osmolarity. MAPK signalling has been implicated in biotic stresses and has also been associated with hormonal responses. The cascade is regulated by various mechanisms, including not only transcriptional and translational regulation but through post transcriptional regulation such as protein-protein interactions. Recent detailed analysis of certain specific MAPK pathways have revealed the specificity of the kinases in the cascade, signal transduction patterns, identity of pathway targets and the complexity of the cascade. However, careful modification of MAPKs can also have beneficial effects like enhanced tolerance against environmental stresses in organisms. A deeper knowledge about regulation of MAPK cascades, e.g. through integrated -omics (transcriptomics, proteomics, phosphoproteomics, metabolomics, cellomics) approaches using publicly available software tools for in silico database analyses, might help to develop novel strategies to improve stress tolerance in plants.

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