

Minireview

Protein kinases in plant growth and defense

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Plants evolved sophisticated strategies to defend themselves against biotic and abiotic stresses. Highly complex signaling networks control these defense responses (Howe and Browse 2008; Wu and Baldwin 2010). Within these networks, the mitogen-activated protein kinase (MAPK) cascades play essential roles (Ichimura et al. 2000; Asai et al. 2002; Teige et al. 2004; Meszaros et al. 2006; Andreasson and Ellis 2010).

MAPKs are well conserved in eukaryotes and they play a key role in transducing extracellular stimuli to intracellular responses (Romeis et al. 2001; Zhang and Liu 2001). Typically, a MAPK cascade consists of a three-kinase module. MAPKs form the terminal components of these cascades, and are activated by MAPK kinases (MAPKKs) via dual phosphorylation of conserved threonine and tyrosine residues. MAPKKs are themselves activated through phosphorylation of conserved serine and/or threonine residues (MAPK Group 2002). The genome of the model plant *Arabidopsis thaliana* encodes 20 MAPKs, 10 MAPKKs and more than 60 MAPKKKs (Andreasson and Ellis 2010). This mismatch between the numbers of MAPKKs and MAPKs suggests that individual MAPKKs must have the capacity to activate more than one MAPK (Andreasson and Ellis 2010). Several recent studies support this scenario. The *Arabidopsis* MAPKs, MPK3 and MPK6, have been shown to be regulated after different stimuli, and MPK3 and MPK6 are phosphorylated by different MAPKKs. They seem to be regulated by the MKK9 (a MAPKK) in ethylene signaling (Yoo et al. 2008). Additionally, both MAPKs are regulated by the MAPKKs, MKK4/MKK5, to confer resistance to bacterial and fungal pathogens (Asai et al. 2002). On the other hand, several MAPKKs can activate the same MAPKs: for example, in yeast two-hybrid assays, MKK1 and MKK2 both interacted with a MAPK, MPK4 (Lee et al. 2008). It is possible that plants need such a large number of proteins in MAPK signaling to fine tune their responses to environmental stresses.

As a model plant, the solanaceous species, *Nicotiana attenuata*, has been intensively studied for its ecological interaction with herbivores for more than fifteen years. The germination of *N. attenuata* is induced by certain compo-

nents of smoke after fire, and thus, this plant is one of the pioneers growing in its natural environment, the Great Basin Desert in Utah, USA. After germination, *N. attenuata* is often attacked by the larvae of the moth species *Manduca sexta* and other lepidopteran caterpillars. Therefore *N. attenuata* has evolved to have a complex system of defense responses to counteract herbivory (Baldwin 1998).

Defense responses against herbivores are classified into indirect and direct defenses. Indirect defenses are traits that attract predators or parasitoids of the herbivores and thereby reduce the herbivore loads (Kessler and Baldwin 2002). After herbivore attack, volatile organic compounds (VOCs) released from plants attract predators and parasitoids in laboratory setups (Dicke and van Loon 2000) and in field studies (Kessler and Baldwin 2001). Direct defenses are any traits (e.g. thorns, silica, trichomes, and secondary metabolites) that affect the susceptibility and/or the performance of attacking herbivores and thus increase plant fitness (Kessler and Baldwin 2002). Secondary metabolites, e.g., alkaloids and phenolics, are generally believed to have functions in stress resistance, including herbivory (Duffey and Stout 1996). They can be classified into three categories: 1) toxic compounds, 2) digestibility reducers and 3) antinutritive compounds (Duffey and Stout 1996). Toxic compounds are for example alkaloids and phenolics. One of the best studied anti-herbivore toxic compounds in tobacco species is the pyridine alkaloid nicotine (Steppuhn et al. 2004). Nicotine binds the acetylcholine receptors in the nervous systems, therefore it is extremely toxic to most animals, although some insects have evolved to be able to detoxify nicotine and even use it for their own defense (Kessler and Baldwin 2002). Proteinase inhibitors have been shown to reduce the ability of herbivores to digest plant material, since they reduce the activity of midgut digestive proteinase enzymes, therefore decreasing larval growth rate and survivorship (Zavala et al. 2008). Polyphenol oxidases are antinutritive enzymes that decrease the value of the wounded plant by cross-linking proteins or catalyzing the oxidation of phenolic secondary metabolites to reactive and polymerizing quinines (Mayer 2006; Mahanil et al. 2008).

The regulation of defense responses is largely controlled by phytohormones. Phytohormones are small molecules which can appear in low concentrations but play a critical role in regulating plant development and responses to environmental stimuli, such as biotic or abiotic stresses (McCourt 1999; Weyers and Paterson 2001; Shakhirova et al. 2002; Nemhauser et al. 2006; Lau and Deng 2010). Known phytohormones are auxin, cytokinins, ethylene (ET), abscisic acid (ABA), gibberellic acids (GA), jasmonates (JAs, jasmonic acid and its derivatives), salicylic acid (SA), strigolactones, and brassinosteroids.

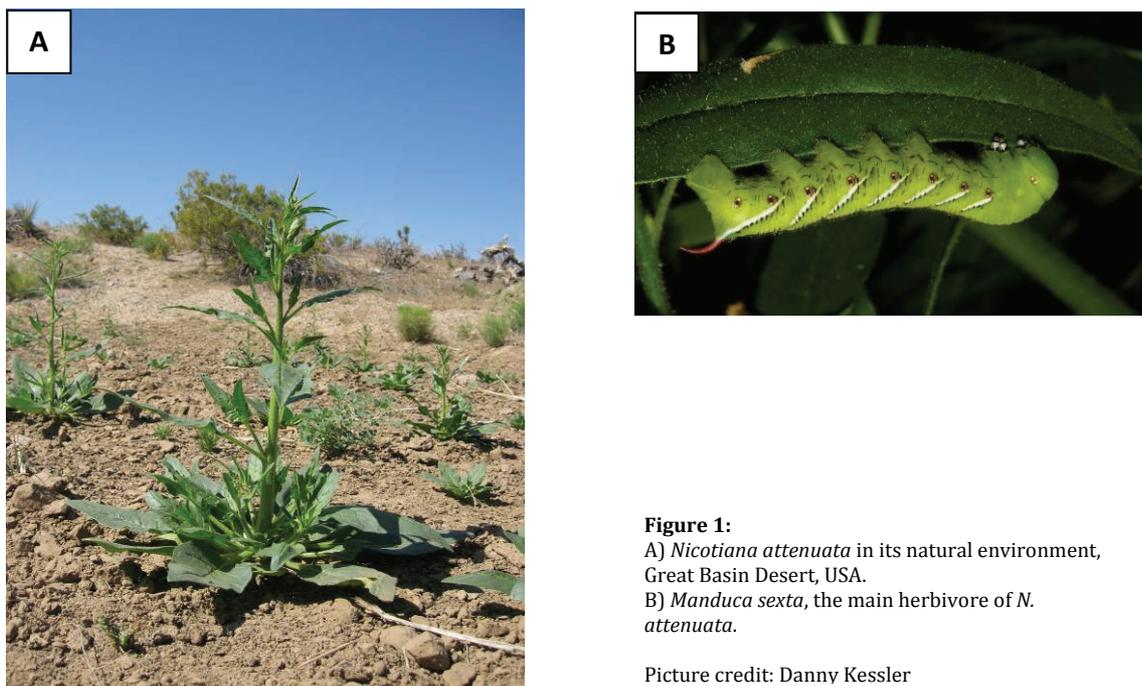


Figure 1:
 A) *Nicotiana attenuata* in its natural environment, Great Basin Desert, USA.
 B) *Manduca sexta*, the main herbivore of *N. attenuata*.

Picture credit: Danny Kessler

The main phytohormone involved in herbivore defense is JA (Wasternack 2007; Howe and Browse 2008; Jander 2008; Wu and Baldwin 2010; Howe 2011). After its release from chloroplast membranes, linolenic acid is modified by lipoxygenase (Vick and Zimmerman 1984), allene oxidase synthase (AOS), and allene oxide synthase (AOC), to form 12-oxo-phytodienoic acid (OPDA) (Vick and Zimmerman 1979). JA is produced in peroxisomes, where OPDA is reduced by OPDA reductase 3 (OPR3) and thereafter three further oxidation reactions (Vick and Zimmerman 1984; Stintzi et al. 2001; Schaller et al. 2004). *N. attenuata* plants attacked by *M. sexta* larvae generate a JA burst, which is induced by specific elicitor compounds, fatty acid-amino acid conjugates (FACs), in *M. sexta* oral secretions (OS), to activate herbivory-specific responses (Halitschke et al. 2001). JA signaling is required to upregulate the activity of trypsin proteinase inhibitor (TPI) in the leaves (Zavala et al. 2004) and to emit volatiles that attract predators of *M. sexta* (Kessler and Baldwin 2001; Paschold et al. 2007). As JA is the main phytohormone regulating defense responses of *N. attenuata*, it is important to understand how plant perceive herbivory and the regulatory mechanism underlying JA biosynthesis. Yet, no receptor has been identified, although the research on metabolism of FACs has provided a deeper insight on herbivore recognition (Bonaventure and Baldwin 2010). It has been shown that two MAPKs, WIPK and SIPK, play an important role in the signaling cascade mediating FAC-induced JA biosynthesis (Wu et al. 2007; Wu and Baldwin 2010). In Heinrich et al. (2011a) two MAPKs, NaMEK2 and NaMCK1, which regulate SIPK and WIPK in a different manner, were identified; NaMEK2 and NaMCK1 also control some aspects of the defense responses of *N. attenuata* against *M. sexta*. In Heinrich et al. (2011b), three more MAPKs, NaNPK2, NaMEK1 and

NaSIPK, which do not activate SIPK, but influence TPI accumulation, were identified.

Another group of kinases acting in the signaling cascades of plants are calcium-dependent protein kinases (CDPKs) (Yoon et al. 1999; Romeis et al. 2000; Romeis 2001; Romeis et al. 2001; Ivashuta et al. 2005). The calcium ion is recognized as a secondary messenger in numerous plant signaling pathways. The information in $[Ca^{2+}]$ changes is decoded by an array of Ca^{2+} -binding proteins resulting in changed gene expression and protein phosphorylation (Sanders et al. 2002). Insect salivary secretions can increase the level of cytosolic Ca^{2+} levels, whereas mechanical damages do not (Maffei et al. 2004). CDPKs constitute a large family of serine/threonine protein kinases. In *Arabidopsis thaliana* 34 CDPK genes have been found in its genome (Cheng et al. 2002). CDPKs are a class of Ca^{2+} sensors, having both a protein kinase domain and a calmodulin-like domain (including an EF-hand Ca^{2+} binding site) in a single polypeptide (Klimecka and Muszynska 2007). Upon insect attack, Arabidopsis CDPKs, CPK3 and CPK13, play a role in transcriptional activation of a plant defensive gene *PDF1.2* (Kanchiswamy et al. 2010). In tobacco plants, NtCDPK2 was suggested to participate in the synthesis of ethylene and jasmonates and in cross-talk with the MAPK cascade activated by pathogen infection (Ludwig et al. 2005).

In *N. attenuata*, four CDPK genes (*CDPK2*, *CDPK4*, *CDPK5* and *CDPK8*) have been shown to be upregulated after simulated herbivore attack (adding oral secretion of *M. sexta* (W+OS) to fresh wounds). Compared with empty vector control plants, in *SIPK*-silenced plants, the transcript levels of *CDPK2*, *CDPK4*, *CDPK5*, and *CDPK8* were altered (Wu et al. 2007). This suggests a function of MAPKs in CDPK transcript regulation. Stably silencing *CDPK4* and *CDPK5* (*CDPK4/5*) leads to highly upregulated defense

responses including elevated JA accumulation and high amount of secondary metabolites (Yang et al., in review). Moreover, plants silenced in *CDPK4/5* showed stunted growth, dark green leaves and had decreased fertility due to abortion of flower buds and flowers. These findings suggest that *CDPK4/5* are not only repressors of *M. sexta*-induced defense responses, but might play an important role in plant development.

Classical phytohormones involved in plant development are auxin (IAA), gibberellic acids (GAs), cytokines, abscisic acid (ABA) and ethylene. Auxin influences the growth of plant organs by a stream that flows from the shoot apex to the tip of the root (Lomax et al. 1995). It has been shown that auxin promotes root growth of Arabidopsis by modulating cellular responses to GA (Fu and Harberd 2003). Cytokines are mainly produced in the roots (Aloni et al. 2004, 2005). From the sites of cytokine production, it moves in specific structural pathways and by different mechanisms to regulate plant development and differentiation (Aloni et al. 2004, 2005). Abscisic acid regulates many processes of plant growth and development, such as seed maturation and germination, seedling growth, flowering and stomatal movement, and is described as a key hormone mediating plant adaption to abiotic stresses like drought, salt and cold stress (Koornneef et al. 1998; Leung and Giraudat 1998; Finkelstein et al. 2002; Cutler et al. 2010). Ethylene is known to modulate Arabidopsis vegetative growth (Wang et al. 2002; Achard et al. 2006). Ethylene regulates vegetative growth, flowering, senescence process, and is also involved in biotic and abiotic stress resistance (Bleecker and Kende 2000).

Bioactive gibberellins control diverse aspects of plant growth and development, including seed germination, stem elongation, leaf expansion and flower and seed development (Yamaguchi 2008). The GA metabolism has been studied intensively and most of the enzymes have been identified. GAs are biosynthesized from geranylgeranyl diphosphate (GGDP), a common C20 precursor for diterpenoids. In Arabidopsis, GA 20-oxidase (*GA20ox*) and GA 3 β -hydroxylase (*GA3ox*) are encoded by a multi gene family. They catalyze the final steps in the formation of bioactive Gas (GA₁ and GA₄) and are downregulated by applying GA (Hedden and Phillips 2000; Olszewski et al. 2002). Plants having loss-of-function mutations in *GA20ox* and *GA3ox* are dwarf (Prat et al. 2000; Sasaki et al. 2002; Sun and Gubler 2004). GAs are perceived by receptor, *GID1* (*GIBBERELLIN INSENSITIVE DWARF1*), and the binding of bioactive GAs to *GID1* induces degradation of *DELLA* proteins, which function as transcriptional repressors (Sun and Gubler 2004). In addition to their function in plant growth regulation, Navarro et al. (2008) demonstrated that *DELLA* proteins modulate the balance between SA and JA signaling. Salicylic acid is another phytohormone, which is involved in pathogen resistance (Kunkel and Brooks 2002). A growing body of evidence suggests that each phytohormone somehow influences the others to obtain the optimum output of plants fitness. It has not been elucidated yet, whether and how JA signaling influences the accumulation of GAs or GA signaling.

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