

DARWIN REVIEW

The interaction of plant biotic and abiotic stresses: from genes to the field

Nicky J. Atkinson* and Peter E. Urwin

Centre for Plant Sciences, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, UK

* To whom correspondence should be addressed. E-mail: nickysj@hotmail.com

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Abstract

Plant responses to different stresses are highly complex and involve changes at the transcriptome, cellular, and physiological levels. Recent evidence shows that plants respond to multiple stresses differently from how they do to individual stresses, activating a specific programme of gene expression relating to the exact environmental conditions encountered. Rather than being additive, the presence of an abiotic stress can have the effect of reducing or enhancing susceptibility to a biotic pest or pathogen, and vice versa. This interaction between biotic and abiotic stresses is orchestrated by hormone signalling pathways that may induce or antagonize one another, in particular that of abscisic acid. Specificity in multiple stress responses is further controlled by a range of molecular mechanisms that act together in a complex regulatory network. Transcription factors, kinase cascades, and reactive oxygen species are key components of this cross-talk, as are heat shock factors and small RNAs. This review aims to characterize the interaction between biotic and abiotic stress responses at a molecular level, focusing on regulatory mechanisms important to both pathways. Identifying master regulators that connect both biotic and abiotic stress response pathways is fundamental in providing opportunities for developing broad-spectrum stress-tolerant crop plants.

Key words: Abiotic stress, biotic stress, hormone signalling, multiple stress, stress combination.

Introduction

Plants have evolved to live in environments where they are often exposed to different stress factors in combination. Being sessile, they have developed specific mechanisms that allow them to detect precise environmental changes and respond to complex stress conditions, minimizing damage while conserving valuable resources for growth and reproduction. Plants activate a specific and unique stress response when subjected to a combination of multiple stresses (Rizhsky *et al.*, 2004b). In light of this, current techniques for developing and testing stress-tolerant plants by imposing each stress individually may be inadequate (Mittler and Blumwald, 2010). This is particularly true for combinations of biotic and abiotic stresses, the signalling pathways of which can act antagonistically (Anderson *et al.*, 2004; Asselbergh *et al.*, 2008b). While valuable, the results of studies investigating stress factors in isolation do not explain the effects of more than one stress on plants. There is an

urgent need for a change of focus in plant stress research, in order to understand the nature of multiple stress responses and to create avenues for developing plants that are resistant to multiple stresses yet maintain high yields. Here the effects of biotic and abiotic stress interaction in plants are reviewed, with an emphasis on elucidating the molecular mechanisms involved.

The challenge of multiple environmental stresses in agriculture

Most crop plants grow in environments that are suboptimal, which prevents the plants from attaining their full genetic potential for growth and reproduction (Bray *et al.*, 2000; Rockstrom and Falkenmark, 2000). This is highlighted by analysing the difference between maximum crop

yields and the average yield for that crop. For example, US wheat yields in a record year can be up to eight times as great as the average yield (Boyer, 1982). The yield difference can largely be explained by unfavourable environmental conditions, which, when creating potentially damaging physiological changes within plants, are known as stresses (Shao *et al.*, 2008). Abiotic stress factors such as heat, cold, drought, salinity, and nutrient stress have a huge impact on world agriculture, and it has been suggested that they reduce average yields by >50% for most major crop plants (Wang *et al.*, 2003). Further to this, plants must defend themselves from attack by a vast range of pests and pathogens, including fungi, bacteria, viruses, nematodes, and herbivorous insects (Hammond-Kosack and Jones, 2000). Each stress elicits a complex cellular and molecular response system implemented by the plant in order to prevent damage and ensure survival, but often at the detriment of growth and yield (Herms and Mattson, 1992).

Current climate prediction models indicate that average surface temperatures will rise by 3–5 °C in the next 50–100 years, drastically affecting global agricultural systems (IPCC, 2007). This will be concurrent with an increased frequency of drought, flood, and heat waves (IPCC, 2008; Mittler and Blumwald, 2010). In particular, warmer, drier summers in mid-continental regions such as central Europe and central Africa are predicted, along with a reduction in growing season in many regions, extensive salinization as sea levels rise, and a decrease in land suitable for agriculture (Easterling *et al.*, 2000; IPCC, 2007, 2008; Morison *et al.*, 2008). A change in variability of rainfall and temperature may itself affect yields as well as adversely affecting nutritional quality of crops (Porter and Semenov, 2005). Climate change will also influence the habitat range of pests and pathogens, with increasing temperature facilitating pathogen spread (Bale *et al.*, 2002; Luck *et al.*, 2011; Madgwick *et al.*, 2011; Nicol *et al.*, 2011). Crop plants are therefore likely to encounter a greater range and number of environmental stresses, which when occurring simultaneously can have severe consequences. The changing climatic conditions, combined with an increasing pressure on global food productivity due to population increase, result in a demand for stress-tolerant crop varieties that has never been greater (Takeda and Matsuoka, 2008; Newton *et al.*, 2011). Understanding the mechanisms of plant responses to multiple simultaneous stresses is therefore crucial in providing opportunities for the development of broad-spectrum stress-tolerant crops.

The importance of studying plant stresses in combination

The ultimate goal of creating stress-tolerant crops either transgenically or through conventional breeding has pervaded almost all aspects of plant science, and is pursued by both public and private sector researchers. Success has already been achieved in many areas. For example, resistance to abiotic stresses has been demonstrated in a variety

of crops through genetic manipulation of transcription factors (TFs), late embryogenesis abundant (LEA) proteins, and antioxidant proteins (Umezawa *et al.*, 2006; Bhatnagar-Mathur *et al.*, 2008). Resistance to plant-parasitic nematodes has been conferred to potato, rice, and banana plants by the expression of transgenes (Fuller *et al.*, 2008). In addition, tolerance to both biotic and abiotic stresses has been achieved. In maize, breeding programmes have led to plants which are tolerant to drought and have additional resistance to the parasitic weed *Striga hermonthica* (Banziger *et al.*, 2006; Badu-Apraku and Yallou, 2009). However, research programmes aimed at developing tolerance to a particular stress do not necessarily test susceptibility to other biotic or abiotic stresses. This can have unforeseen consequences, as improved varieties may respond unpredictably when grown in field conditions (McKersie *et al.*, 1999; Mohamed *et al.*, 2001; Mittler, 2006; Collins *et al.*, 2008). Examples include: a variety of cassava bred for resistance to *Cassava mosaic virus* (CMV), which was later found to be a greater target for the whitefly pest *Bemisia tabaci* (Otim *et al.*, 2006); new drought-tolerant aerobic rice varieties that were particularly susceptible to nematode infection, perhaps due to their increased root length (Kreye *et al.*, 2009); and transgenic cotton plants expressing the *Bacillus thuringiensis* (Bt) insecticidal protein *Cry* that showed a reduction in the level of the protein during periods of high temperature, elevated CO₂ levels, or drought, leading to decreased resistance to pests (Chen *et al.*, 2005; Dong and Li, 2007). Transgenic plants overexpressing a proline biosynthesis enzyme (P5C) accumulate this osmoprotectant during drought and are thus resistant to osmotic stress (Kishor *et al.*, 1995; Bray *et al.*, 2000; Chaves *et al.*, 2003). However, Rizhsky *et al.* (2004b) found that under a combination of drought and heat stress, plant cells accumulated sucrose instead of proline, perhaps to protect hyperactive and therefore susceptible mitochondria from the build-up of potentially toxic P5C. In the transgenic plants an added heat stress may therefore counteract any osmoprotective benefit.

An increasing volume of evidence from field, laboratory, and molecular studies suggests that plants respond to a specific combination of stresses in a non-additive manner, producing effects that could not have been predicted from the study of either stress individually (Mittler, 2006; Rizhsky *et al.*, 2004b). For example, a report by Mittler *et al.* (2006) described that in the US between 1980 and 2004 the total agricultural losses attributed to drought were worth US\$20 billion, but total losses due to drought combined with a heat wave totalled US\$120 billion, suggesting that the presence of a second stress factor can exacerbate the detrimental effects of the first. Therefore, in order to develop crops that thrive and maintain a high yield in field conditions, an integrated approach should be adopted whereby resistance traits are tested under a range of stress treatments (Mittler and Blumwald, 2010). It has been proposed that truly to characterize the response of plants to multiple stresses, it is crucial to impose the stresses simultaneously and treat each set of environmental conditions as an entirely new stress (Mittler, 2006).

Plants must produce a tailored response to specific multiple stress conditions, as in many cases the individual stresses would normally elicit opposing reactions. For example, heat stress usually causes plants to open their stomata in order to cool the leaves, but under drought conditions this would be disadvantageous as more water would be lost (Rizhsky *et al.*, 2004b). Similarly, increased transpiration caused by heat stress could enhance uptake of salt or heavy metals, heightening the damage from these factors (Mittler and Blumwald, 2010). Plants must efficiently balance resource allocation between growth and defence against stress, as responding to stress can be costly and reduce fitness in terms of growth and yield (Herms and Mattson, 1992; Tian *et al.*, 2003; Smith and Stitt, 2007; Bechtold *et al.*, 2010). This cost is highlighted by examples where the experimental transgenic expression of a stress-responsive gene confers stress tolerance but to the detriment of growth and yield (Bechtold *et al.*, 2010). For instance, constitutive overexpression of *Arabidopsis thaliana DREB1A* or rice *DREB1A* confers freezing and dehydration tolerance (Kasuga *et al.*, 1999; Liu *et al.*, 1998; Dubouzet *et al.*, 2003). The constitutive expression of a pigeonpea proline-rich protein in *Arabidopsis* confers tolerance to osmotic, salt, and heat stress, but produces plants that are stunted in size (Priyanka *et al.*, 2010). The cost to plants of defence is therefore likely to be reduced if specific genes and compounds have roles in several different stress responses, a potential explanation for the overlap between stress response pathways (Herms and Mattson, 1992; Bergelson and Purrington, 1996; Asselbergh *et al.*, 2008b). This would explain the findings that certain molecular signalling pathways, TFs, and effector proteins are activated by both biotic and abiotic stresses (Mengiste *et al.*, 2003; Narusaka *et al.*, 2004; Vannini *et al.*, 2006; Zhang *et al.*, 2006; AbuQamar *et al.*, 2009; Dubos *et al.*, 2010), and that secondary metabolites such as flavonoids accumulate in response to and provide protection from a wide range of stresses (English-Loeb *et al.*, 1997; Treutter, 2006; Cle *et al.*, 2008; Atkinson *et al.*, 2011).

The occurrence of simultaneous biotic and abiotic stresses presents an added degree of complexity, as the responses to these are largely controlled by different hormone signalling pathways that may interact and inhibit one another (Anderson *et al.*, 2004; Asselbergh *et al.*, 2008b). Often, the exposure of plants to a pest or pathogen increases the effects of an abiotic stress such as water deficit (Cockfield and Potter, 1986; English-Loeb, 1990; Khan and Khan, 1996; English-Loeb *et al.*, 1997; Smit and Vamerli, 1998; Audebert *et al.*, 2000), whereas long-term abiotic stress can weaken plant defences and cause enhanced pathogen susceptibility (Amtmann *et al.*, 2008; Goel *et al.*, 2008; Mittler and Blumwald, 2010). Despite this, few reports in the literature have focused on understanding the interaction between biotic and abiotic stresses. A range of case studies combining biotic and abiotic stress are examined in the next section, followed by analysis of the molecular mechanisms controlling stress interaction.

Evidence from the field and laboratory of the interaction of biotic and abiotic stresses

Different stress factors occurring in combination may be considered additive or interactive (Niinemets, 2010). When the presence of an initial or previous stress alters a plant's normal response to a second stress as a result of an acclimation response, the stress factors can be said to interact. The deleterious interactive effect on crops of two different abiotic stresses has been well studied, and was recently reviewed by Mittler and Blumwald (2010). Heat and drought stress in particular can cause disproportionate damage to crops compared with either stress individually (Keles and Oncel, 2002; Rizhsky *et al.*, 2002; Mittler, 2006; Barnabas *et al.*, 2008). However, when examining the effects of an abiotic stress with simultaneous impact of a pathogen or herbivore, both positive and negative interactions have been observed depending on the timing, nature, and severity of each stress. An increase in temperature can create a negative interactive effect by lowering resistance to bacterial, viral, fungal, and nematode pathogens: in wheat, higher mean temperatures observed over a 6 year experimental period correlated with heightened susceptibility to the fungus *Cochliobolus sativus* (Sharma *et al.*, 2007). In tobacco and *Arabidopsis*, hypersensitive response (HR)- and *R*-gene-mediated defence responses to *Pseudomonas syringae* and viral elicitors are compromised at high temperatures, allowing increased growth of these pathogens (Wang *et al.*, 2009). The nematode and aphid resistance gene *Mi-1.2* is also known to be inactivated at temperatures >28 °C, promoting a higher infection rate (Dropkin, 1969).

Drought stress can cause detrimental effects to plant pathogen resistance. In both sorghum and the common bean, drought-treated plants had a higher susceptibility to the charcoal rot fungus *Macrophomina phaseolina* (Diourte *et al.*, 1995; Mayek-Perez *et al.*, 2002). Similarly, drought stress increased the spread of fungal and bacterial leaf scorch symptoms on date palms and the *Parthenocissus quinquefolia* vine (McElrone *et al.*, 2001; Suleman *et al.*, 2001). Exposure of *Arabidopsis* to drought stress allowed greater infection levels of an avirulent isolate of *P. syringae* (Mohr and Cahill, 2003).

In contrast, abiotic stress may also interact positively with pathogen stress. In barley, increasing salt-induced osmotic stress was directly correlated with resistance to powdery mildew (Wiese *et al.*, 2004), while drought stress can enhance resistance to the fungus *Botrytis cinerea* in tomato (Achu *et al.*, 2006). Pathogens may also actively interfere with plant water relations in order to increase pathogenesis. For example, they may cause stomatal closure to reduce water loss from infected tissues, thus having a positive effect on plant tolerance against abiotic stress (Goel *et al.*, 2008; Beattie, 2011). The herbivore *Spodoptera exigua* showed a reduced ability to feed on drought-stressed tomato leaf tissue, which contained higher levels of defence compounds as a result of the abiotic stress (English-Loeb *et al.*, 1997). Infection with viruses can actually provide protection from drought stress (Xu *et al.*, 2008). In virus-infected tobacco,

beet, and rice, drought symptoms appeared later and leaves maintained water longer than their uninfected counterparts. Metabolite analysis suggested that this protection may be due to the virus-induced accumulation of osmoprotectants and antioxidants such as anthocyanins. A similar effect is observed with certain beneficial microorganisms. Timmusk and Wagner (1999) were amongst the first to discover this, after finding that plants treated with the rhizobacterium *Paenibacillus polymyxa* showed an enhanced resistance to drought and further bacterial attack, an effect associated with the expression of the *ERD15* (*EARLY RESPONSE TO DEHYDRATION 15*) gene. Now many types of bacteria and arbuscular mycorrhizal fungi are known to enhance stress tolerance in a range of crop species, by producing antioxidants, suppressing ethylene production, stabilizing soil structure, increasing osmolyte production, and improving abscisic acid (ABA) regulation, amongst others (Alami *et al.*, 2000; Saravanakumar and Samiyappan, 2007; Aroca *et al.*, 2008; Kohler *et al.*, 2008; Grover *et al.*, 2011). The employment of such microbes may provide an alternative strategy to genetic engineering and plant breeding for delivering swift but effective increases in crop stress tolerance (Xu *et al.*, 2008; Grover *et al.*, 2011).

Soil-borne pathogens have not been studied so extensively in stress research, perhaps due to difficulties in data acquisition or the destructive sampling methods required, but they are nevertheless important (Eastburn *et al.*, 2010). Infection with plant-parasitic nematodes can exacerbate or counteract the effects of abiotic stress on plants, as their parasitism in roots severely disrupts plant water relations (Bird, 1974; Haverkort *et al.*, 1991; Smit and Vamerli, 1998). Figure 1 shows an example of the positive interactive effect of drought stress and nematode infection on rice plants. In this case, the addition of nematodes ameliorated the severity of the drought stress. Several studies have been

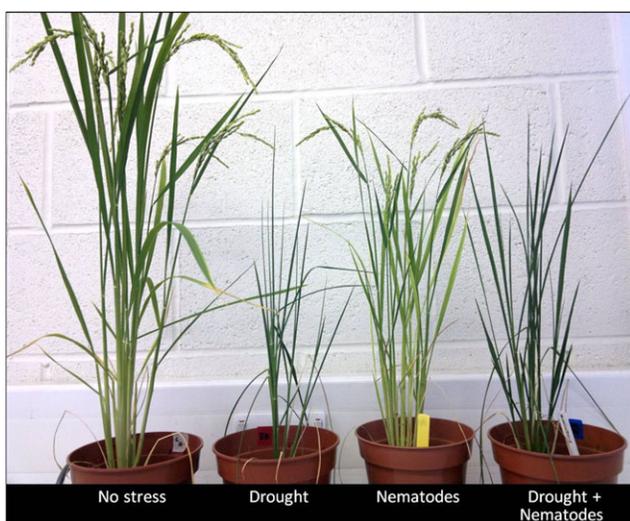


Fig. 1. Growth of rice under combined biotic and abiotic stress conditions. Plants are shown after exposure to drought stress, infection with the plant-parasitic nematode *Meloidogyne graminicola*, or the two stresses in combination.

carried out to examine the effect of combined nematode and drought stress on plant growth and development. In The Ivory Coast the nematode *Heterodera sacchari* increased drought-related losses in upland rice by contributing to reduced leaf water potential, stomatal conductance, and leaf dry weight (Audebert *et al.*, 2000). A similar study investigated the effect of drought and the cyst nematode *Globodera pallida* on water use efficiency in potato (Haverkort *et al.*, 1991). Both factors were found to affect growth negatively, although the simultaneous effect of both stresses was not additive, perhaps because the infected plants used less water, thus reducing drought stress. *Globodera pallida* has also been shown to cause retardation in potato root development, which in turn had the effect of reducing drought tolerance (Smit and Vamerli, 1998). A study of the interaction of *Meloidogyne incognita* infection and mineral pollutants on tomato crops in India revealed a synergistic effect whereby nematode infection worsened the effects of pollution on foliage, while increasing pollution caused greater root galling (Khan and Khan, 1996). However, field studies have often been unable to separate the effects of soil hydrology, irrigation, and nematode community dynamics from the effects of nematode parasitism itself (Coyne *et al.*, 2001).

Having found that the effects of simultaneous biotic and abiotic stresses may interact both positively and negatively, the subsequent parts of this review aim to uncover the genes and molecular mechanisms involved in regulating this response.

Transcriptome analysis of multiple stress responses

The investigation of plant molecular responses to multiple stresses has often focused on overlapping transcriptional patterns. To this effect, several studies have been carried out in which different groups of plants are exposed to either one stress or another in parallel, and their gene expression patterns compared. Overlapping sets of genes that are regulated by both stresses are then identified and proposed to represent a generalized stress response or points of cross-talk between signalling pathways (Kreps *et al.*, 2002; Seki *et al.*, 2002; De Vos *et al.*, 2005; Swindell, 2006; Kilian *et al.*, 2007; Huang *et al.*, 2008). It has been speculated that these genes may be targets for improving stress tolerance in crop plants (Seki *et al.*, 2002; Denby and Gehring, 2005; Swindell, 2006). For example, following comparison of the transcriptome response of *Arabidopsis* plants to nine different abiotic stresses using Affymetrix ATH1 microarrays, 67 genes were found to be commonly regulated by every stress, suggesting that there was a universal component of the response to each condition (Swindell, 2006). A similar experiment investigated the expression of cytochrome P450 genes in response to various abiotic stresses, pathogens or hormone treatments. Genes were identified that were commonly induced by both biotic and abiotic stress, and therefore may be important in regulating

cross-talk between pathways (Narusaka *et al.*, 2004). In chickpea, the responses to biotic and abiotic stresses were compared using a 758-probe microarray. Several shared responses were observed, in particular between high salinity stress and a fungal pathogen (Mantri *et al.*, 2010).

However, such studies may be of limited use in understanding plant responses to multiple simultaneous stresses, as when stresses occur in combination certain genes are activated that are not induced by either stress individually (Rizhsky *et al.*, 2002, 2004b; Mittler, 2006). In both *Arabidopsis* and tobacco, recent transcriptome analysis has shown that the molecular response of plants to simultaneous heat and drought stress is not additive. The stress combination results in a new pattern of gene expression that could not have been predicted by studying either stress in isolation, including the induction of numerous specifically regulated genes (Rizhsky *et al.*, 2002, 2004b). Among the genes specifically regulated by the two stresses in *Arabidopsis* are those encoding heat shock proteins (HSPs), proteases, lipid biosynthesis enzymes, and starch degrading enzymes, as well as MYB TFs, protein kinases, and defence proteins involved in protection against oxidative stress (Rizhsky *et al.*, 2004b).

Further transcriptome studies in various species have identified genes, hormones, and processes important in controlling plant response to multiple abiotic or multiple biotic stresses and provided targets for the improvement of stress tolerance (Voelckel and Baldwin, 2004; Hewezi *et al.*, 2008; Priyanka *et al.*, 2010; Wang *et al.*, 2010; Grigorova *et al.*, 2011). A combination of high light and high temperature activated a specific subset of differentially expressed genes in sunflower (Hewezi *et al.*, 2008). In wheat, simultaneous drought and heat stress activated a pattern of HSP expression that is non-additive and could not be predicted from the study of either stress individually (Grigorova *et al.*, 2011). At a physiological level, the imposition of drought and heat stress negatively affected wheat photosynthetic rates to a greater extent than each one alone (Wang *et al.*, 2010). Analysis of the transcriptome in tobacco following infestation by two insect herbivores, a sap-feeding mirid (*Tupiocoris notatus*) and a chewing hornworm (*Manduca sexta*), revealed a specific transcriptional effect when the two herbivores were applied together compared with when each was applied separately (Voelckel and Baldwin, 2004). This supports the existence of *trans*-activating factors that reorganize gene expression depending on the nature of the stress. Furthermore, gene expression patterns were different if the herbivores were applied sequentially compared with in parallel, suggesting a system of priming whereby the transcriptome exhibits a long-term change following biotic attack and serves as a kind of immunological memory. Another study analysed peanut plants infected with the fungus *Aspergillus parasiticus* and exposed to drought (Luo *et al.*, 2005). Using two expressed sequence tag (EST) cDNA libraries, 42 genes were found to be up-regulated in response to both the fungus and drought simultaneously, whereas 52 genes were up-regulated by drought alone. As root damage due to drought is advantageous for this

pathogen, it is proposed that the fungus may be able to repress ABA and drought signalling in order to achieve a higher infection rate.

Transcriptome data of this kind provide a molecular explanation for the observed non-linear effects of multiple stresses on plant stress resistance described above. Rather than produce a stock response to each pathogen or abiotic stress, plants respond to the precise environmental conditions encountered and instigate a new programme of gene expression accordingly. However, despite increasing interest in the effects of simultaneous biotic and abiotic stresses on plants, no studies have yet documented whole-genome transcriptome changes resulting from any such stress combination.

Despite the quantity of data produced and the useful insights that can be inferred, transcriptomic studies do not provide a comprehensive description of changes in cellular protein activity (Margolin and Califano, 2007; Deyholos, 2010). Research suggests that the correlation between TF and target gene mRNA is low, and that the activity of most TFs is likely to be controlled post-transcriptionally or through phosphorylation (Herrgard *et al.*, 2003). In addition, correlation between proteomic data and transcript abundance measured by microarrays is surprisingly low ($R = 0.24$) (Fu *et al.*, 2009). In order to obtain a more accurate description of components in stress signalling pathways, metabolic and proteomic analyses are becoming increasingly utilized (Koussevitzky *et al.*, 2008; Shulaev *et al.*, 2008; Urano *et al.*, 2009; Hofmann *et al.*, 2010). The integration of these data with transcriptome results will provide the most powerful tool for characterizing such complex plant processes (Deyholos, 2010; Urano *et al.*, 2010). In addition, the study of hormone mutants has vastly increased our understanding of multiple stress responses.

Hormone signalling pathways controlling stress interaction

Abiotic stress responses are largely controlled by the hormone ABA, while defence against different biotic assailants is specified by antagonism between the salicylic acid (SA) and jasmonic acid (JA)/ethylene signalling pathways. However, recent findings suggest that ABA acts both synergistically and antagonistically with biotic stress signalling, creating a complex network of interacting pathways with cross-talk at different levels (Fig. 2) (Fujita *et al.*, 2006; Asselbergh *et al.*, 2008b; Yasuda *et al.*, 2008). ABA is therefore likely to be central in the fine-tuning of observed responses to simultaneous biotic and abiotic stresses. Treatment with ABA increases susceptibility in *Arabidopsis* to an avirulent *P. syringae* strain (Mohr and Cahill, 2003), in tomato to *B. cinerea* and *Erwinia chrysanthemi* (Audenaert *et al.*, 2002; Asselbergh *et al.*, 2008a), in rice to the blast fungus *Magnaportha grisea* (Koga *et al.*, 2004), and in potato to the pathogens *Phytophthora infestans* and *Cladosporium cucumerinum* (Henfling *et al.*, 1980). In accordance with this, a lack of ABA can induce a higher level of pathogen

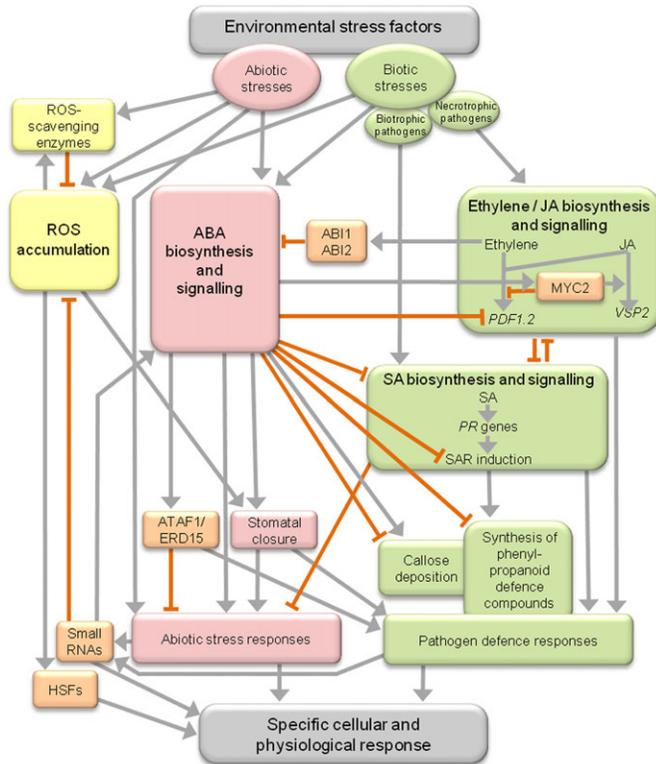


Fig. 2. The role of plant hormones in regulating the interaction between biotic and abiotic stress. The schematic diagram shows cross-talk occurring between hormones, transcription factors, and other regulatory components when biotic and abiotic stresses occur concurrently. This complex network of interactions allows plants to respond in a highly specific fashion to the exact combination of environmental stresses encountered. Grey arrows show induction or positive regulation, while orange bars show inhibition or repression. Events characteristic of abiotic stress responses are shown in pink, while those characteristic of biotic stress responses are shown in green. Transcription factors and other regulatory genes are represented by orange boxes. ROS, reactive oxygen species; ABA, abscisic acid; JA, jasmonic acid; SA, salicylic acid; *PR*, pathogenesis-related; SAR, systemic acquired resistance; HSF, heat shock factor.

resistance (Asselbergh *et al.*, 2008a). For example, the ABA-insensitive *Arabidopsis* mutants *abi1-1* and *abi2-1* showed resistance to the oomycete *Peronospora parasitica* and the fungal pathogen *Fusarium oxysporum*, respectively (Mohr and Cahill, 2003; Anderson *et al.*, 2004), while the tomato *sitiens* mutant, which has reduced ABA levels, showed an increased accumulation of SA-dependent defence transcripts such as *PRI*, as well as enhanced tolerance to *B. cinerea* (Audenaert *et al.*, 2002; Asselbergh *et al.*, 2007). ABA treatment represses the systemic acquired resistance (SAR) pathway both upstream and downstream of SA induction in *Arabidopsis* and tobacco, as well as inhibiting the accumulation of crucial defence compounds such as lignins and phenylpropanoids (Fig. 2) (Mohr and Cahill, 2007; Yasuda *et al.*, 2008; Kusajima *et al.*, 2010). In turn, SA can also interfere with abiotic stress signalling. The exogenous application of SA in maize leads to drought

susceptibility (Nemeth *et al.*, 2002), while the artificial induction of SAR in *Arabidopsis* leads to the suppression of abiotic stress responses (Yasuda *et al.*, 2008). In rice, resistance to the rice blast fungus *M. grisea* is mediated by a precise balance between ABA and SA levels (Jiang *et al.*, 2010). ABA also antagonizes JA and ethylene defence signalling, as shown by the ABA-mediated repression of defence genes such as *PDF1.2*, an effect that cannot be reversed by the application of JA or ethylene (Anderson *et al.*, 2004). Ethylene treatment, in turn, activates ABI1 and ABI2, two negative regulators of ABA signalling (Asselbergh *et al.*, 2008b).

Despite these observations, ABA can also have a positive effect on pathogen defence systems (Asselbergh *et al.*, 2008b; Ton *et al.*, 2009). Melotto *et al.* (2006) found that ABA-induced stomatal closure was a defensive strategy of plants to prevent microbial invasion through open stomata, a process that also required intact SA signalling. Furthermore, ABA is necessary for β -aminobutyric acid (BABA)-induced callose deposition during defence against fungal pathogens (Ton and Mauch-Mani, 2004), although interestingly ABA can block bacterial-induced callose production (de Torres-Zabala *et al.*, 2007).

A new model has been proposed regarding the multifaceted role of ABA in pathogen response, whereby the influence of ABA depends on the time scale of infection and also the nature of the attacker (Ton *et al.*, 2009). The model refers to three distinct phases of pathogen infection. In the first, ABA causes stomatal closure, increasing resistance to penetration by pathogens such as bacteria, and thus having a positive effect on the defence response. At this stage, ABA antagonizes SA, JA, and ethylene pathways in order to save resources, as their effects are not yet required. In the second phase, post-invasion defences centre on callose deposition to strengthen cell walls, a process that is aided by ABA during fungal infection but repressed during bacterial infection. During phase three of infection, PAMPs (pathogen-associated molecular patterns) induce the hormones SA, JA, and ethylene and long-distance signals to regulate a broad spectrum of defensive compounds. The ABA-inducible genes *ERD15* and *ATAF1* have been identified as switches that may activate ABA-dependent biotic stress responses at the expense of abiotic responses (Kariola *et al.*, 2006; Jensen *et al.*, 2008; Ton *et al.*, 2009). However, increased ABA levels arising from abiotic stress conditions may repress the SA, JA, and ethylene responses even during phase three. This hypothesis provides a mechanism for the control of ABA over both biotic and abiotic stress signalling, and helps to explain previous conflicting data (Asselbergh *et al.*, 2008b). To complicate matters further, recent research has found that ABA can have either a positive or a negative effect on bacteria-induced callose deposition, depending on other growth conditions such as light and glucose levels, thus switching its effect on the defence response according to the environmental situation (Luna *et al.*, 2011). Such research emphasizes the need for caution when drawing conclusions from pathogen resistance assays.

ABA is now considered a global regulator of stress responses that can dominantly suppress pathogen defence pathways, thus controlling the switch in priority between the response to biotic or abiotic stress and allowing plants to respond to the most severe threat (Asselbergh *et al.*, 2008b). ABA production may therefore be the crucial factor in determining how plants respond to multiple stresses.

Convergent signalling pathways in multiple stress responses

Biotic and abiotic stress signal transduction results from a complex arrangement of interacting factors (Fujita *et al.*, 2006) (Fig. 3). Certain gene products are crucial to both biotic and abiotic stress signalling, and may therefore control the specificity of the response to multiple stresses (Mauch-Mani and Mauch, 2005). Transcriptomic and genetic analyses have greatly increased our knowledge of such processes.

Transcription factors

TFs are of key importance in generating specificity in stress responses. Their manipulation provides one of the greatest

opportunities for conferring multiple stress tolerance transgenically, as they control a wide range of downstream events (Pardo, 2010; Xu *et al.*, 2011). A list of TFs that may be crucial in controlling the response to biotic and abiotic stresses is given in Table 1. MYC2 (also called JIN1) is central to the interaction between biotic and abiotic signalling pathways (Anderson *et al.*, 2004). It is a positive regulator of specifically JA-induced defence genes but represses genes induced by combined JA/ethylene signalling (Anderson *et al.*, 2004; Pieterse *et al.*, 2009). It acts as a key repressor of the SA pathway (Laurie-Berry *et al.*, 2006). MYC2 has also been found to be activated by ABA, and *myc2* mutants lack ABA-responsive gene expression (Abe *et al.*, 2003). Therefore MYC2 may act as a central-regulator by which ABA controls biotic stress signalling pathways (Anderson *et al.*, 2004; Asselbergh *et al.*, 2008b; Pieterse *et al.*, 2009). This partial synergy between ABA and JA signalling may explain the situations in which pathogen resistance is enhanced by abiotic stress, such as the finding that in barley drought stress increases resistance to *Blumeria graminis* (Wiese *et al.*, 2004), or that in *Arabidopsis* ABA is necessary for defence responses against the oomycete *Pythium irregulare* (Adie *et al.*, 2007).

A large, functionally diverse group, the MYB family of TFs is becoming increasingly associated with the control of both biotic and abiotic stress responses, in particular the regulation of phenylpropanoid biosynthesis pathways (Dubos *et al.*, 2010). In a microarray study of combined drought and heat stress in *Arabidopsis*, certain MYB TFs were specifically induced by the stresses in combination but not by either stress individually, supporting a role for them in differentiating between precise stress conditions (Rizhsky *et al.*, 2004b). MYB96 is induced by drought stress, and promotes ABA-dependent stress tolerance by inducing the biosynthesis of cuticular wax (Seo *et al.*, 2011). Interestingly, MYB96 is also required for ABA-dependent SA biosynthesis and, when overexpressed, causes increased *PR* gene expression and resistance against pathogens, acting as a link between these two hormones in governing broad-spectrum stress tolerance (Seo and Park, 2010). Antagonism between regulators of the flavonol biosynthesis pathway, MYB12 and MYB4, allows plants to manipulate the pathway depending on which stress combination is encountered (Schenke *et al.*, 2011). UV-B stress alone stimulates MYB12-regulated flavonol production, while the addition of the bacterial elicitor flg22 induces MYB4, repressing this process and allowing the production of defence compounds including lignin and phytoalexins. The MYB factor *BOS1* in *Arabidopsis* is also required for both biotic and abiotic stress responses (Mengiste *et al.*, 2003). The function of MYB TFs is well conserved between species. Showing high homology to *Arabidopsis* BOS1, the tomato SIAIM1 is required for resistance to *B. cinerea* and tolerance to abiotic stresses (AbuQamar *et al.*, 2009). Its involvement in regulating ion homeostasis during oxidative stress may underpin its importance in a wide range of stresses. The MYB factor TaPIMP1 from wheat confers tolerance to pathogens, drought, and salt stresses when overexpressed in

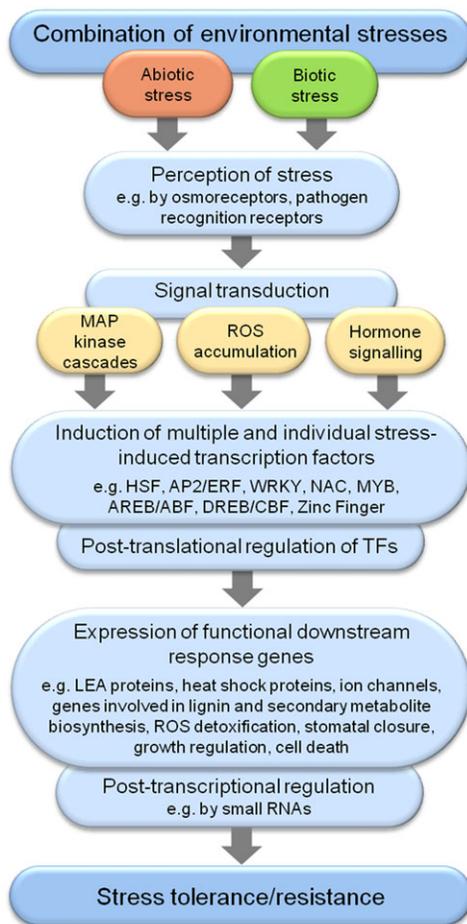


Fig. 3. Key events in the signal transduction pathway activated in response to combined biotic and abiotic stresses.

Table 1. Transcription factors with a potential role in the interaction between biotic and abiotic stress signalling pathways

Gene	Type	Species	Induced by	Potential mechanisms of action	References
<i>MYB2</i>	MYB	<i>Arabidopsis</i>	Drought, ABA	Regulates ABA- and JA-inducible genes.	Abe <i>et al.</i> (2003); Shinozaki <i>et al.</i> (2007)
<i>MYB4</i>	MYB	<i>Arabidopsis</i>	UV-B, flg22	Negative regulator of UV-B protective flavonol synthesis. Represses flavonol pathway in response to flg22 allowing synthesis of pathogen defence compounds.	Jin <i>et al.</i> (2000); Schenke <i>et al.</i> (2011)
<i>MYB12</i>	MYB	<i>Arabidopsis</i>	UV-B	Positive regulator of UV-B-induced flavonol production. Down-regulated following additional flg22 treatment.	Schenke <i>et al.</i> (2011)
<i>MYB96</i>	MYB	<i>Arabidopsis</i>	Drought, flg22	Regulates drought-responsive cuticular wax formation and promotes SA biosynthesis.	Seo and Park (2010); Seo <i>et al.</i> (2011)
<i>BOS1</i>	MYB	<i>Arabidopsis</i>	<i>Botrytis cinerea</i>	Required to restrict spread of necrotrophic pathogens and provide tolerance to abiotic stresses (water deficit, salinity, oxidative stress).	Mengiste <i>et al.</i> (2003)
<i>MYB4</i>	MYB	Rice	Cold stress	Overexpression in <i>Arabidopsis</i> confers resistance to abiotic (cold, drought, salt, ozone) and biotic stresses (viruses, bacteria, fungi). Confers drought stress and virus resistance in tomato.	Vannini <i>et al.</i> (2004, 2006, 2007)
<i>AIM1</i>	MYB	Tomato	<i>B. cinerea</i> , <i>P. syringae</i> , NaCl, ABA	Potentially integrates responses to biotic and abiotic stresses by modulating ABA signalling and ion fluxes.	AbuQamar <i>et al.</i> (2009)
<i>PIMP1</i>	MYB	Wheat	<i>Bipolaris sorokiniana</i> , drought	Modulates response to biotic and abiotic stresses. Confers tolerance to both when expressed in tobacco.	H.X. Liu <i>et al.</i> (2011)
<i>MYC2</i>	bHLH	<i>Arabidopsis</i>	Dehydration, ABA, wounding	Central in cross-talk between hormone signalling pathways. Activated by ABA, it acts as a positive regulator of JA signalling and suppresses SA responses.	Abe <i>et al.</i> (2003); Anderson <i>et al.</i> (2004); Laurie-Berry <i>et al.</i> (2006)
<i>ATAF1</i>	NAC	<i>Arabidopsis</i>	<i>Blumeria graminis</i>	ABA-inducible factor that represses ABA signalling during pathogen infection.	Jensen <i>et al.</i> (2008)
<i>ATAF2</i>	NAC	<i>Arabidopsis</i>	Wounding, SA, JA, drought, dark, <i>P. syringae</i>	Integrates wounding and pathogen defence responses.	Delessert <i>et al.</i> (2005)
<i>NTL6</i>	NAC	<i>Arabidopsis</i>	Cold	A cold-activated inducer of <i>PR</i> gene expression and disease resistance.	Seo <i>et al.</i> (2010)
<i>RD26</i>	NAC	<i>Arabidopsis</i>	Drought, NaCl, ABA, JA	Positively regulates ABA-responsive genes and mediates cross-talk between ABA and JA signalling pathways.	Fujita <i>et al.</i> (2004)
<i>NAC6</i>	NAC	Rice	Dehydration, cold, NaCl, wounding, JA, H ₂ O ₂ , <i>Magnaporthe grisea</i>	An inducer of biotic and abiotic stress responses that has a negative effect on growth when overexpressed.	Nakashima <i>et al.</i> (2007)
<i>NAC4</i>	NAC	Wheat	JA, ABA, ET, <i>Puccinia striiformis</i> , salinity, wounding, cold	A transcriptional activator in biotic and abiotic signalling pathways.	Xia <i>et al.</i> (2010)
<i>DEAR1</i>	AP2/ERF	<i>Arabidopsis</i>	<i>P. syringae</i> , cold	Negatively regulates components of the SA-mediated pathogen response and DREB/CBF freezing tolerance pathways.	Tsutsui <i>et al.</i> (2009)
<i>ERFLP1</i>	AP2/ERF	Hot pepper	ET, wounding, NaCl, <i>Xanthomonas axonopodis</i>	Targets binding domains in genes involved in pathogen defence and salt tolerance.	Lee <i>et al.</i> (2004)
<i>BIERF1-4</i>	ERF	Rice	<i>M. grisea</i> , SA, NaCl, cold, drought, wounding, benzothiadiazote	Positive regulators of disease resistance responses that may also regulate tolerance to abiotic stresses.	Cao <i>et al.</i> (2006)
<i>ERF3</i>	AP2/ ERF	Soybean	NaCl, drought, ABA, ET, SA, JA, soybean mosaic virus	A positive regulator of defence and abiotic stress genes, causing biotic and abiotic stress tolerance when expressed in tobacco.	G.Y. Zhang <i>et al.</i> (2009)
<i>TS1</i>	ERF	Tobacco	NaCl, SA, ethephon	Positive regulator of genes in salt tolerance and PR gene-associated pathogen defence pathways	Park <i>et al.</i> (2001)
<i>OPBP1</i>	AP2/ EREBP	Tobacco	<i>Phytophthora cryptogea</i> elicitor, NaCl, JA	Overexpression gives tolerance to fungal, bacterial, and salt stress.	Guo <i>et al.</i> (2004)
<i>AREB1</i>	ABF	Tomato	Drought, NaCl	Functions in ABA-mediated abiotic stress and pathogen response signalling.	Orellana <i>et al.</i> (2010)

Table 1. Continued

Gene	Type	Species	Induced by	Potential mechanisms of action	References
WRKY45	WRKY	Rice	ABA, SA, NaCl, mannitol, dehydration, cold, heat, <i>Pyricularia oryzae</i> , <i>Xanthomonas oryzae</i>	Increases pathogen resistance in rice and <i>Arabidopsis</i> when overexpressed, as well as inducing ABA-responsive abiotic stress tolerance genes.	Shimono <i>et al.</i> (2007); Qiu and Yu (2009)
WRKY82	WRKY	Rice	<i>M. grisea</i> , <i>Rhizoctonia solani</i> , JA, ethephon, wounding, heat	Regulates responses to biotic and abiotic stresses through the JA/ET signalling pathway.	Peng <i>et al.</i> (2011)
ZAT7	Zinc-finger	<i>Arabidopsis</i>	Salinity, heat, oxidative stress, heat, wounding	Suppresses a repressor of defence responses to a wide range of stresses, including WRKY70, a mediator between JA and SA signalling.	Rizhsky <i>et al.</i> (2004a); Ciftci-Yilmaz <i>et al.</i> (2007)
ZAT12	Zinc-finger	<i>Arabidopsis</i>	Oxidative stress, heat, wounding, cold, NaCl, drought, ABA, auxin, high light, biotic stresses	A central regulator connecting reactive oxygen and abiotic stress signalling. Regulates genes responsive to high light and oxidative stress.	Rizhsky <i>et al.</i> (2004a); Davletova <i>et al.</i> (2005); Vogel <i>et al.</i> (2005)
HSFA1b	HSF	<i>Arabidopsis</i>	Heat shock	Regulates basal resistance to biotic and abiotic stresses and maintains growth rate under stress.	Mullineaux <i>et al.</i> (2011)
HSFA2	HSF	<i>Arabidopsis</i>	High light, heat, H ₂ O ₂	H ₂ O ₂ -induced early regulator of defence genes.	Nishizawa <i>et al.</i> (2006)

ABA, abscisic acid; ET, ethylene; JA, jasmonate; SA, salicylic acid.

tobacco (H.X. Liu *et al.*, 2011), while the rice MYB4 gene confers broad-spectrum stress tolerance when overexpressed in *Arabidopsis* or tomato (Vannini *et al.*, 2006, 2007). Conserved cysteine residues in the MYB family of TFs suggests that MYB activity may be controlled by cellular redox status (Dubos *et al.*, 2010). The oxidation or *S*-nitrosylation of cysteine residues would alter domain structure and prevent DNA binding, thus providing a mechanism for control following biotic or abiotic stress-induced reactive oxygen species (ROS) production (Heine *et al.*, 2004).

NAC and AP2/ERF TFs have long been associated with stress signalling, and recent discoveries suggest that they may make excellent targets for improving broad-spectrum tolerance in crops through genetic engineering (Nakashima *et al.*, 2007; Xu *et al.*, 2011). The *Arabidopsis* NAC TF RD26 is induced by JA and pathogens, as well as by ABA, drought, and salinity, and may regulate ROS detoxification genes (Fujita *et al.*, 2004). There is evidence that ATAF1 in *Arabidopsis* acts as a switch to repress the effect of ABA during pathogen infection (Mauch-Mani and Flors, 2009). In mutant *ataf1* plants ABA biosynthesis genes were up-regulated and resistance to penetration by the pathogen *B. graminis* was compromised (Jensen *et al.*, 2008). In rice, OsNAC6 is a transcriptional activator during both biotic and abiotic stresses, and confers tolerance to dehydration, high salinity, and rice blast when overexpressed, albeit with a yield penalty (Nakashima *et al.*, 2007). The wheat *TaNAC4* gene is induced by the rust stripe fungus, high salinity, wounding, and cold stress (Xia *et al.*, 2010). Its expression also responds to treatment with the hormones ABA, ethylene, and methyl jasmonate, suggesting that *TaNAC4* regulates cross-signalling between stress response pathways. TSI1 from tobacco is an AP2/ERF TF whose action straddles both pathogen response and abiotic stress pathways (Park *et al.*, 2001). It induces the expression of *PR* genes and can confer resistance to salt and

pathogenic bacteria. Certain AP2/ERFs from tomato and soybean can enhance multiple stress tolerance when expressed in tobacco, as described in a recent review by Xu *et al.* (2011).

Other recently identified TFs that act in both pathways include tomato SIAREB1, which confers resistance to salt and drought stress as well as activating defence-related genes (Orellana *et al.*, 2010); pepper RFP1, which functions as a defence regulator and confers osmotic stress tolerance (Hong *et al.*, 2007; Asselbergh *et al.*, 2008b); two WRKY TFs in rice, WRKY82 and WRKY45, which are both responsive to biotic and abiotic stresses (Qiu and Yu, 2009; Peng *et al.*, 2011); and a transcriptional repressor of *DREB* genes, DEAR1, which when activated represses freezing tolerance but enhances pathogen tolerance (Tsutsui *et al.*, 2009). Many TFs confer a growth impediment when overexpressed, indicative of a shift in balance between allocation of resources into stress protection rather than growth (Nakashima *et al.*, 2007; AbuQamar *et al.*, 2009; Tsutsui *et al.*, 2009). In order to overcome this problem transgenes often need to be expressed under a stress-inducible promoter (Kasuga *et al.*, 1999; Qiu and Yu, 2009).

Mitogen-activated protein kinase (MAPK) cascades

MAPK cascades are crucial in eukaryotes for transducing the perception of environmental stimuli into internal signalling pathways (Rodriguez *et al.*, 2010). Plants have a particularly large number of MAPK components, allowing for the control over a wide range of stress response pathways (Zhang *et al.*, 2006). During biotic stress, plant transmembrane receptors such as FLS2 detect PAMPs and trigger MAPK cascades in order to establish pathogen response signalling (Nakagami *et al.*, 2004; Chinchilla *et al.*, 2007). During abiotic stress, MAPK cascades such as the MEKK1/MKK2/MPK4/MPK6 pathway are induced, for instance following activation of the transmembrane osmoreceptor

ATHK1 in *Arabidopsis* (Urao *et al.*, 1999; Teige *et al.*, 2004; Rodriguez *et al.*, 2010). Downstream targets of MAPK cascades include TFs, for example those in the WRKY family, and hormone response factors such as ETHYLENE INSENSITIVE3 (EIN3) (Andreasson and Ellis, 2010). MAPK cascades are particularly important in controlling cross-talk between stress responses, as many MAPKs are activated by more than one type of stress or plant hormone, and are thus able to integrate different signals (Rohila and Yang, 2007; Andreasson and Ellis, 2010). For example, *Arabidopsis* MPK6 functions in the response to ethylene synthesis, cold and salt stress, the pathogen signalling, and stomatal control (Rodriguez *et al.*, 2010). In rice at least five of the 17 identified *MAPK* genes are inducible by both biotic and abiotic stresses (Rohila and Yang, 2007), and certain MAPKs can directly influence both pathways. Of these, OsMAPK5 positively regulates the response to cold, drought, and salt stress, at the same time suppressing the expression of defence transcripts such as *PR* genes (Xiong and Yang, 2003). Overexpression of OsMAPK5 confers increased abiotic stress tolerance, while RNA interference (RNAi) lines are more resistant to fungal and bacterial pathogens. In tomato, the response to UV-B, a wounding signal, and a pathogen elicitor are all transduced using shared MAPK signalling components, including LeMPK1 and LeMPK2 (Holley *et al.*, 2003). Exposure to one stress can cause desensitization of the MAPK cascade to another stress, a phenomenon resulting from the transient refractory state of MAPKs after activation, underlining the similarity between responses (Yalamanchili and Stratmann, 2002). In cotton, the MAPK GhMPK16 has been shown to regulate components of biotic and abiotic signalling pathways, and when overexpressed in *Arabidopsis* confers resistance to pathogens while negatively affecting drought tolerance (Shi *et al.*, 2011). MAPK cascades may be activated by and indeed regulate the production of ROS such as H₂O₂, which play a crucial role in signal cross-talk (Apel and Hirt, 2004; Fujita *et al.*, 2006; Zhang *et al.*, 2006; Takahashi *et al.*, 2011). Signal specificity of MAPK cascades is controlled by scaffold proteins such as CTR1, which can tether certain MAPK proteins together, and by spatio-temporal restrictions (Nakagami *et al.*, 2004; Andreasson and Ellis, 2010; Rodriguez *et al.*, 2010).

Heat shock factors (HSFs)

HSPs bind and stabilize proteins that have become denatured during stress conditions, and function as molecular chaperones which prevent protein aggregation (Bartels and Sunkar, 2005). Specific combinations of HSPs are induced following different types of abiotic stress, and they play an important role in protecting plants from oxidative stress (Wang *et al.*, 2003; Rizhsky *et al.*, 2004b). Recent research shows that HSPs function in the specific response of crop plants such as maize and wheat to combined heat and drought stress (Hu *et al.*, 2010; Grigorova *et al.*, 2011). The expression of HSPs is controlled by HSFs, of which there are a large number in *Arabidopsis* compared with animals

(von Koskull-Doring *et al.*, 2007). HSFs may act as molecular sensors to detect the presence of ROS such as H₂O₂ and activate downstream stress-responsive genes accordingly (Miller and Mittler, 2006; Hu *et al.*, 2010). A particular candidate for redox sensing in *Arabidopsis* is HSFA4a, due to its rapid induction in response to H₂O₂ and its transcriptional control over ROS-scavenging enzymes (Miller and Mittler, 2006). The functional diversity between HSFs may reflect a crucial role in allowing plants to respond to different environmental conditions (Rizhsky *et al.*, 2004b; Miller and Mittler, 2006). In rice, the induction patterns of HSPs and HSFs following stress treatment with drought, heat, cold, and salt showed some overlap, but also a specific response to each condition (Hu *et al.*, 2009). Rizhsky *et al.* (2004b) discovered that certain HSPs were specifically induced in *Arabidopsis* by a combination of drought and heat stress and that these changes were reflected by differences in expression levels of HSFs between stress treatments. Expression analysis of all 21 *Arabidopsis* HSFs revealed a different pattern for each of nine abiotic stresses, which differed depending on the tissue sampled (Miller and Mittler, 2006; von Koskull-Doring *et al.*, 2007). In addition, different biotic stresses elicited a unique combination of HSFs (von Koskull-Doring *et al.*, 2007). The specific combination of HSFs activated may therefore direct the outcome of the stress response. Providing confirmation of this, the ectopic overexpression of the *HSFA2* gene in *Arabidopsis* conferred tolerance to a combination of environmental stresses (Nishizawa *et al.*, 2006). The HSFA1 group of four *Arabidopsis* TFs (a, b, d, and e) are now thought to act as master regulators of the heat shock response. They also contribute to resistance against other abiotic stresses, and are essential for the maintenance of normal growth and productivity under stress conditions (Liu *et al.*, 2011; Mullineaux *et al.*, 2011; Yoshida *et al.*, 2011). *HSFA1b* regulates >500 genes, controlling tolerance to drought, extreme temperature, and a range of biotrophic pathogens, as well as being a determinant of seed yield (Mullineaux *et al.*, 2011). Activity of *HSFA1b* is mainly controlled post-translationally, perhaps providing an explanation for its late discovery in the study of plant stress. The targeting of this newly discovered regulatory system provides exciting possibilities for crop improvement, as when *HSFA1b* was overexpressed in oilseed rape it conferred stress resistance phenotypes as well as maintaining yield productivity (Mullineaux *et al.*, 2011).

Reactive oxygen species

There is increasing evidence that ROS play a central role in mediation between biotic and abiotic stress responses (Pastori and Foyer, 2002; Fujita *et al.*, 2006; Ton *et al.*, 2009). ROS are critical to both types of stress response, but function differently in each. Low levels of ROS accumulate constantly as by-products of metabolism, but their concentration increases during abiotic stress conditions such as osmotic stress, salinity, and high light. To minimize damage caused by these potentially harmful molecules,

plants produce antioxidants and ROS-scavenging enzymes (Apel and Hirt, 2004; Miller *et al.*, 2010). In contrast, plants actively generate ROS following pathogen infection, in a process known as the oxidative burst. This limits pathogen spread by contributing to the hypersensitive response and cell death, in this case requiring the coordinated down-regulation of ROS-scavenging mechanisms (De Gara *et al.*, 2003; Apel and Hirt, 2004; Torres, 2010).

Plants have also adapted to use ROS as stress signal transduction molecules, and a unique footprint of ROS-responsive genes is induced by each type of biotic and abiotic stress (Gadjev *et al.*, 2006). H₂O₂ is produced by membrane-bound NADPH oxidases immediately on pathogen infection or wounding, then diffuses into cells and activates various plant defences, for example in distal leaf tissue following wounding (Orozco-Cardenas and Ryan, 1999; Apel and Hirt, 2004). ROS production is furthermore required for ABA-driven stomatal closure. ABA induces the NADPH oxidases *AtRbohD* and *AtRbohF* which generate ROS in guard cells as signalling intermediaries (Torres, 2010). This commonality between biotic and abiotic stress-induced ROS production may contribute towards the positive effect of ABA on early pathogen response.

However, ABA can also have a negative effect on ROS-mediated pathogen defence, as demonstrated by the ABA-deficient tomato *sitiens* mutant. These plants accumulate H₂O₂ rapidly following infection by *B. cinerea*, leading to a stronger defence response and greater resistance to the pathogen compared with the wild type (Asselbergh *et al.*, 2007). The ABA biosynthesis pathway is tightly linked to ascorbate levels and therefore to the redox status of cells (Muller-Moule *et al.*, 2002). It has been proposed that the build-up of ABA precursors in the *sitiens* mutant could disrupt redox homeostasis and cause the observed beneficial increase in ROS accumulation (Ton *et al.*, 2009).

Precise coordination of ROS production and scavenging mechanisms during combined biotic and abiotic stress is clearly necessary, and certain TFs integrate ROS-scavenging mechanisms in response to multiple types of stress. ZAT12 is an *Arabidopsis* zinc-finger TF that is responsive to high H₂O₂ levels and is induced by wounding, and abiotic and biotic stress. It induces genes such as ascorbate peroxidase (*APX1*), and when overexpressed conferred tolerance to oxidative stress, freezing, and high light (Rizhsky *et al.*, 2004a; Davletova *et al.*, 2005; Vogel *et al.*, 2005; Fujita *et al.*, 2006). Similarly, ZAT7 is activated in response to oxidative stress, and confers tolerance to salt, cold, and oxidative stress when expressed ectopically (Rizhsky *et al.*, 2004a; Ciftci-Yilmaz *et al.*, 2007). ZAT7 also induces the expression of various defence transcripts, including *WRKY70*, a gene that modulates cross-talk between the SA and JA pathogen response pathways (Li *et al.*, 2006; Ciftci-Yilmaz *et al.*, 2007). Evidence suggests that the *APX1* enzyme itself is crucial in the response to multiple stresses. It was found to accumulate in *Arabidopsis* specifically in response to combined heat and drought stress, but not in response to either stress individually (Koussevitzky *et al.*, 2008). Plants lacking the *APX1* gene have a significantly lower survival rate under

the stress combination compared with wild-type plants, although survival under a single stress is unaffected. The cytosolic location of *APX1* suggests that dual heat and drought stress may cause a critical build-up of H₂O₂ in the cytosol, leading to cell injury and death if not dealt with (Koussevitzky *et al.*, 2008). The cellular localization of ROS production and metabolism may determine specificity in ROS signalling, as different scavenging enzymes and antioxidants are prevalent in each cellular compartment (Miller *et al.*, 2010). A newly discovered gene, PENTATRICOPEPTIDE REPEAT PROTEIN FOR GERMINATION ON NaCl (*PGN*), highlights the role of ROS in the interaction between biotic and abiotic stress responses (Laluk *et al.*, 2011). There is evidence that *PGN* regulates ROS homeostasis in the mitochondria by interacting with genes such as alternative oxidase 1 (*AOX1*). In the *pgn* mutant, impaired ROS regulation caused susceptibility to necrotrophic fungal pathogens, high salt, and glucose stress, and led to increased levels of ROS and ABA. Overexpression of *PGN* led to similar stress susceptibility phenotypes as in *pgn* plants, indicating that tight regulation of *PGN* is necessary for the control of mitochondrial ROS levels in both biotic and abiotic stresses (Laluk *et al.*, 2011).

As stresses often occur in combination, and the relationship between ROS signalling mechanisms in different stress responses is complex, identifying master regulators of ROS metabolism may provide the best candidates for generating broad-spectrum stress tolerance (Miller *et al.*, 2010).

Small RNAs

Our understanding of the complexity of plants' responses to stress has been enhanced by the discovery of small non-coding RNA species that play crucial regulatory roles (Sunkar *et al.*, 2007; Ruiz-Ferrer and Voinnet, 2009). The levels of these small RNAs change in response to different abiotic stresses in *Arabidopsis*, providing new avenues for the investigation of plant stress signalling (Sunkar and Zhu, 2004). MicroRNAs (miRNAs), which are derived from long single-stranded RNA folded into a hairpin structure, and small interfering RNAs (siRNAs), which are derived from double-stranded RNA and can act in both *cis* and *trans*, silence genes post-transcriptionally by targeting mRNA for degradation or repressing translation (Mallory and Vaucheret, 2006; Sunkar *et al.*, 2007). The advent of high-throughput sequencing technology has facilitated rapid identification of small RNAs (Fahlgren *et al.*, 2007; Xin *et al.*, 2010), and several categories are now known to be involved in stress responses, as reviewed by Ruiz-Ferrer and Voinnet (2009), Sunkar *et al.* (2007), and Mallory and Vaucheret (2006). For example, in *Arabidopsis*, the miR399 miRNA is induced in response to low phosphate stress. It controls phosphate homeostasis by suppressing the expression of a ubiquitin-conjugating enzyme, thus allowing uptake and mobilization of phosphate and preventing phosphate starvation (Fujii *et al.*, 2005; Chiou *et al.*, 2006). Although not generally well conserved between species, stress-responsive miRNAs have been identified in a variety

of plants. In the grass *Brachypodium distachyon*, the induction and suppression of miRNAs occur as a result of cold stress (J.Y. Zhang *et al.*, 2009). In rice a network of oxidative stress-responsive miRNAs regulate processes such as programmed cell death, nutrient transport, and auxin homeostasis (Li *et al.*, 2011), while the siRNAs siR441 and siR446 positively regulate ABA signalling and tolerance to abiotic stress (Yan *et al.*, 2011). In the legume *Medicago truncatula* the drought-induced production of MtDCL1 and MtAGO1, enzymes that regulate the production and processing of miRNAs, provides a mechanism for the regulation of these small RNA species (Capitao *et al.*, 2011). Improvement of stress tolerance by manipulation of miRNA regulation has also been demonstrated. Transgenic *Arabidopsis* plants expressing a form of the chloroplastic superoxide dismutase *CSD2* that is resistant to suppression by mi398 showed higher ability to detoxify superoxide radicals and thus resistance to oxidative stress (Sunkar *et al.*, 2006).

The ability of miRNAs to modulate events in ROS regulation may explain their function in both biotic and abiotic stress response pathways. The expression of 11 soybean miRNAs was investigated in response to water deficit and infection with soybean rust fungus. All miRNAs were differentially regulated by each stress, usually in an opposite direction (Kulcheski *et al.*, 2011). One miRNA, MIR-Seq11, targets a peroxidase protein that is involved in metabolism of H₂O₂ during oxidative stress, potentially inhibiting its translation or causing mRNA decay. The down-regulation of MIR-Seq11 during biotic stress may therefore provide protection from ROS during pathogen infection. Differential expression between drought-tolerant and drought-susceptible cultivars was also observed. MIR-Seq11 was up-regulated in the drought-susceptible cultivar but not in those which were drought tolerant, suggesting that miRNA control of ROS scavenging could also be a factor in determining susceptibility of these plants to drought (Kulcheski *et al.*, 2011). In wheat, analysis of miRNA expression in response to heat stress and infection with the powdery mildew fungus *Erysiphe graminis* revealed that members of the same miRNA family were differentially regulated by the stresses (Xin *et al.*, 2010). Some were induced by heat but suppressed by the pathogen, while others were induced by both stresses. The unique pattern of miRNA production may therefore provide specificity in controlling stress signalling.

A newly discovered class of siRNAs called nat-siRNAs can regulate both biotic and abiotic stress responses (Mallory and Vaucheret, 2006; Ruiz-Ferrer and Voinnet, 2009). These are derived from natural antisense genes that overlap on opposite strands in the genome, and are formed by the annealing of the sense and antisense transcripts (Sunkar *et al.*, 2007). For example nat-siRNAs derived from the antisense gene pair *PC5DH-SRO5* control proline levels and thus tolerance to salt in *Arabidopsis* (Borsani *et al.*, 2005). In response to salt stress, *SRO5* is transcriptionally activated and a corresponding nat-siRNA is produced, which targets the mRNA of the proline degradation gene

PC5DH for destruction. In response to recognition of the *P. syringae* effector AvrPt2, a nat-siRNA called nat-siRNAATGB2 is specifically induced, which has the effect of down-regulating a putative constitutively active negative regulator of defence (Katiyar-Agarwal *et al.*, 2006).

The control of gene expression by small RNAs may provide a crucial mechanism for regulating the growth and reproduction of plants experiencing stress conditions (Sunkar *et al.*, 2007). This hypothesis is supported by the observation that many stress-responsive small RNAs are also involved in developmental processes, and that disruption of miRNA signalling in *Arabidopsis* can result in delayed flowering time, reduced fertility, leaf defects, and a reduced number of lateral roots (Achard *et al.*, 2004; Mallory *et al.*, 2004; Guo *et al.*, 2005; Sunkar *et al.*, 2007).

Controlling specificity in molecular stress interactions

As well as the regulatory processes described so far in this review, the complex control of specificity in stress signalling is enhanced by a variety of additional cellular interactions. TFs do not bind indiscriminately to every gene with a matching response element, as there may be thousands of such sites across the genome (Vaahtera and Brosche, 2011). Instead, specificity can be generated by TFs forming into homo- or heterodimers, which then bind to a pair of response elements at an appropriate distance from each other, or by the co-operation of bridging or scaffold proteins which direct TFs to the correct response elements (Baudry *et al.*, 2004; Weltmeier *et al.*, 2006; Vaahtera and Brosche, 2011). In addition, TFs may be regulated themselves through redox modification of cysteine residues that can prevent transport into the nucleus, phosphorylation, or protein degradation (Spoel *et al.*, 2010; Vaahtera and Brosche, 2011). These systems allow eukaryotes an extremely high level of control over cellular processes, generating a large number of downstream signalling options without having to produce such high numbers of TFs in the nucleus that overcrowding occurs and TFs cannot easily associate with their target sequence (Vaahtera and Brosche, 2011). One mechanism for enabling a rapid TF response is that of proteolytic activation, in which membrane-bound TFs are cleaved by stress-responsive proteases allowing re-localization of the active subunit into the nucleus. For example, the membrane-bound NTL6 TF becomes cleaved in response to cold stress, and travels to the nucleus where it activates cold-responsive *PR* genes, integrating the responses to cold and pathogens (Seo *et al.*, 2010). The over-expression of *NTL6* in *Arabidopsis* leads to pathogen resistance, while plants with reduced NTL6 activity are susceptible to pathogens at cold temperatures. This illustrates a means by which plants protect themselves from pathogens during cold times of year, a system also thought to occur in grass species such as winter rye (Yu *et al.*, 2001). Transcriptional activation of response elements also requires chromatin remodelling, a process that can be achieved

through stress-induced histone modification (Zhou *et al.*, 2005; Sridha and Wu, 2006). Plant mechanisms for increasing signalling specificity have been recently reviewed by Vaahtera and Brosche (2011).

Perspectives: seeing plant stress research in a new light

Hundreds of studies investigating the effect of individual and combinatorial stresses have allowed us to piece together the complex network of molecular interactions controlling plant stress responses. Plants activate both specific and non-specific stress responses as a reaction to adverse environmental conditions, allowing them to maximize efficiency in responding to the exact set of conditions encountered, at the same time as conserving resources for growth. Signal specificity is achieved through the precise interplay between components of each pathway, particularly the hormones ABA, SA, and JA, TFs, HSFs, ROS, and small RNAs. With so many interacting factors it is easy to see how the effect of multiple stresses on an individual resistance response can be unpredictable. Traditionally, individual plant stress factors have been studied as isolated stimuli that trigger linear signalling pathways. It is clear that this model is no longer sufficient, and both biotic and abiotic stress pathways are inextricably linked in a broad network of molecular interactions.

One of the ultimate aims of plant stress research is to provide targets for the improvement of stress tolerance in crop plants. With the forecast changes in climatic conditions, novel stress combinations are likely to occur in agricultural systems in many parts of the world, presenting new challenges in creating multiple stress-tolerant crops (Easterling *et al.*, 2000; Newton *et al.*, 2011). The development of such plants will depend on understanding crucial stress-regulatory networks and the potential effects of different combinations of adverse conditions. Studies of multiple stress responses in *Arabidopsis* and other species have revealed several possible avenues for exploration. Common threads have been identified between biotic and abiotic signalling pathways, which may lead to their antagonistic nature. Master regulatory genes that act in both biotic and abiotic stress response systems are excellent candidates for manipulating stress tolerance (Baena-Gonzalez and Sheen, 2008; Miller *et al.*, 2010). HSFs such as those in the HSFA1 and HSFA2 families control a large number of downstream stress-responsive genes and have shown promise in conferring tolerance to multiple stresses (H.C. Liu *et al.*, 2011; Mullineaux *et al.*, 2011). Members of the MYC, MYB, and NAC TF families are also potential targets, as they are involved in controlling antagonism between hormone-mediated abiotic stress and pathogen response pathways. Research has already shown that their manipulation can confer tolerance to biotic and abiotic stresses in several species (Vannini *et al.*, 2006; AbuQamar *et al.*, 2009; Seo and Park, 2010; H.X. Liu *et al.*, 2011). Controlling ROS homeostasis genes may also be able to affect tolerance

to a wide range of stresses, due to the involvement of ROS in both abiotic stress and pathogen stress.

The pyramiding of transgenes has proven successful in conferring tolerance to a particular stress, for example to drought in wheat (Wei *et al.*, 2011), to salt stress in tobacco (Duan *et al.*, 2009), to nematodes in potato (Urwin *et al.*, 2003), and to insects in chickpea (Mehrotra *et al.*, 2011). Genetically modified crops have been approved with up to three pyramided transgenes, conferring resistance to two different biotic stresses, for example a virus- and insect-resistant potato developed by Monsanto, and the area of land cultivated with crops containing pyramided transgenes is rising steadily (Halpin, 2005). The pyramiding of several genes may therefore provide further opportunities for creating broad-spectrum stress-tolerant plants (Witcombe *et al.*, 2008).

Another lesson that can be learnt from the extensive study of plant stress responses is that experiments should be carried out in conditions that relate closely to natural or field conditions (Deyholos, 2010; Mittler and Blumwald, 2010). Plants' efficiency in sensing and responding to each unique set of environmental conditions means that different methods of imposing stress can lead to drastically different transcriptional profiles (Bray, 2004). Discrepancies between results of similar experiments show that changes in growth parameters such as light or sugar levels can significantly affect plant stress response priorities (Luna *et al.*, 2011). Therefore, in order to provide a model for crop stress responses, an integrated approach should be adopted whereby researchers aim to mimic a field stress situation in terms of growth media, duration, and severity of stress, timing of stress, and nutrient availability (Mittler and Blumwald, 2010). In addition, it is now clear that plant varieties that have been developed with improved stress tolerance should be tested under the full range of stress combinations that are likely to occur in the field, rather than each stress individually.

In recent years, the necessity for a change in focus in plant abiotic stress research has become apparent. As plants have finite resources which must be balanced between growth and defence against stresses, often both natural and induced stress tolerance comes with a growth or yield penalty, making it agriculturally disadvantageous (Herms and Mattson, 1992; Baldwin, 1998; Liu *et al.*, 1998; Kasuga *et al.*, 1999; Dubouzet *et al.*, 2003; Tian *et al.*, 2003; Priyanka *et al.*, 2010). Rather than developing crops that can survive extreme stress events, it may therefore be more beneficial to focus on producing crops which are stress tolerant but which maintain high photosynthesis, growth rates, and yield (Condon *et al.*, 2004; Morison *et al.*, 2008; Bechtold *et al.*, 2010; Mullineaux *et al.*, 2011). The C24 genotype of *Arabidopsis* exhibits such traits (Bechtold *et al.*, 2010). This accession exhibits constitutive expression of SA-induced defences which allow high levels of resistance against *P. syringae* and *Hyaloperonospora arabidopsidis*, but, unlike mutant genotypes with constitutive SA responses, C24 suffers no yield loss. It also has a greater water use efficiency, meaning that it requires less water than other

accessions to provide the same seed yield, and is drought tolerant. This finding suggests that it may be possible to create plants with broad-spectrum stress tolerance without affecting yield, and continuing studies are being carried out to determine the genetic basis for this beneficial trait (Bechtold *et al.*, 2010). The homeostasis of energy levels also provides a link between stress responses and maintenance of growth. Energy deprivation in plants results from most types of stress as well as nutrient starvation and darkness (Smith and Stitt, 2007). The *Arabidopsis* protein kinase SnRK1 acts as a sensor for energy depletion, and restores homeostasis through large-scale transcriptional reprogramming, thus enabling the continuation of growth and metabolism (Baena-Gonzalez and Sheen, 2008). Amongst its targets are a wide range of general stress-responsive genes involved in both pathogen and abiotic stress tolerance. The manipulation of energy sensors such as SnRK1 could therefore play an important role in maintaining photosynthesis and yield during stress conditions. Targeting of miRNAs that act both in stress responses and in regulation of growth and development may provide further possibilities (Sunkar *et al.*, 2007). The challenge for plant scientists in the 21st century will be to develop stable multiple stress tolerance traits in agronomically important crop plants, thus improving yields particularly in areas with adverse environmental conditions, and contributing to global food security.

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