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Tackling Drought Stress: RECEPTOR-LIKE KINASES Present New Approaches

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Global climate change and a growing population require tackling the reduction in arable land and improving biomass production and seed yield per area under varying conditions. One of these conditions is suboptimal water availability. Here, we review some of the classical approaches to dealing with plant response to drought stress and we evaluate how research on RECEPTOR-LIKE KINASES (RLKs) can contribute to improving plant performance under drought stress. RLKs are considered as key regulators of plant architecture and growth behavior, but they also function in defense and stress responses. The available literature and analyses of available transcript profiling data indeed suggest that RLKs can play an important role in optimizing plant responses to drought stress. In addition, RLK pathways are ideal targets for nontransgenic approaches, such as synthetic molecules, providing a novel strategy to manipulate their activity and supporting translational studies from model species, such as *Arabidopsis thaliana*, to economically useful crops.

INTRODUCTION

“We need a Blue Revolution in agriculture that focuses on increasing productivity per unit of water—more crop per drop,”

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United Nations Secretary General Kofi Annan declared (Pennisi, 2008; United Nations, 2008).

Global climate change is predicted to lead to extreme temperatures and severe drought in some parts of the world, while other parts will suffer from heavy storms and periodic flooding. These conditions will have a dramatic impact on crop growth and productivity, will threaten the societal sustainability (coupled to an increasing global population), and will generate serious challenges for human welfare (Aussenac, 2000; Parmesan and Yohe, 2003; Lobell et al., 2008). Even in Europe, future climate

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change is expected to be problematic, resulting more often in dry springs and rainy summers in northern Europe and longer dry periods in the south. For example, in the European heat wave of 2003, crop production was reduced by around 30% (Ciais et al., 2005). Existing measures, such as protecting the soil with polyethylene cover or by extensive irrigation, have negative environmental impacts and are expensive. The plastic used is durable, but its manufacture requires chemical pollutants and fossil fuels, while extensive irrigation results in decreased soil quality and affects water resources (Oosterbaan, 1988; Wittwer, 1993; Ma et al., 2003; Athar and Ashraf, 2009). In addition, increased land use for biofuel crops will have a negative impact on available land for food crops and on forest lands (Campbell et al., 2008). Therefore, improving biomass production and seed yield per area under suboptimal water availability due to drought and other abiotic stresses by improving the plants themselves is now even more pressing. Here, we highlight how work with peptide ligands and RECEPTOR-LIKE KINASES (RLKs) can play an essential role in addressing this issue. We provide examples of how RLKs integrate developmental and environmental networks and illustrate the potential of RLKs and their associated peptide ligands to enhance drought tolerance.

PLANT RESPONSE TO DROUGHT

The capacity of a given plant to alter its physiology, morphology, and/or phenology is called phenotypic plasticity and allows it to tolerate, avoid, or escape a certain stress condition (Grime et al., 1986). Plant responses to soil water deficit have been extensively investigated at developmental, physiological, and molecular levels (Passioura, 1996; Bray, 1997; Shinozaki and Yamaguchi-Shinozaki, 2000), and the complex nature of growth regulation under stress conditions has been highlighted (Hirayama and Shinozaki, 2010).

In response to a moderate drought scenario, plants use strategies to reduce transpiration, conserve water, and explore enlarged soil volumes to maintain water supply: Partial stomatal closure is induced, leaves are produced at slower rates, and shoot growth generally is decelerated (Figure 1), while, apart from some cases where lateral root growth is strongly inhibited by withholding water, root growth is maintained or even accelerated (Westgate and Boyer, 1985; Vartanian et al., 1994; Passioura, 1996; Spollen et al., 2000; van der Wee et al., 2000; Granier et al., 2006). These responses are coordinated and form parts of a drought avoidance strategy that allows plants to bridge transient periods of drought and to survive more severe and persistent drought conditions by premature flowering and reproduction. At the cellular scale, cell division and endoreduplication are reduced. Cell expansion can be maintained or decreased, depending on the maintenance of turgor and cell wall extensibility regulated by phytohormones like abscisic acid (ABA) and other local and systemic factors involved in coordination of the drought responses

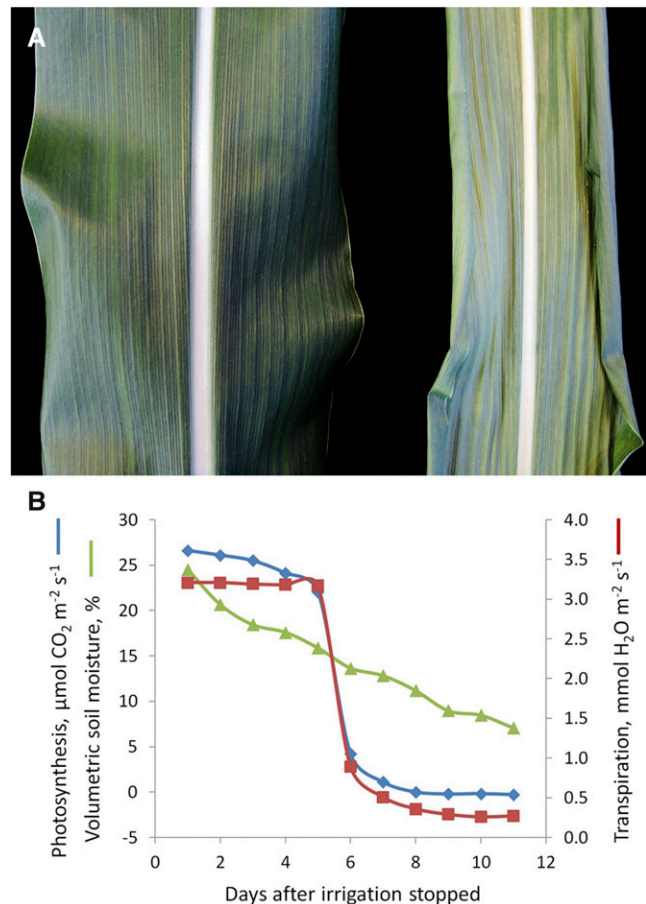


Figure 1. Impact of Water Depletion on Leaf Development and Rate of Photosynthesis.

(A) Two leaf surfaces of the maize inbred line B73 are shown at the same developmental stage. The left leaf of a daily watered plant is fully expanded. The leaf at the right from a plant that was depleted of water for 10 d contains a smaller leaf surface area and less chlorophyll, stomata are closed, and leaf margins are curled to avoid water loss. Watering of plants at this stage leads to full recovery.

(B) Soil moisture continuously decreases after water depletion. Below a critical moisture of ~15% (4th to 5th day after water depletion) rates of photosynthesis and transpiration drop dramatically to ~10% of well-watered rates. (Figure courtesy of Manfred Gahrz.)

(Aguirrezabal et al., 2006; Cookson et al., 2006; Valliyodan and Nguyen, 2006). However, each individual response and the additive effect of several responses does not necessarily lead to drought tolerance (Tardieu, 2012). It is therefore tedious to select a promising individual plant response as a target for improving drought tolerance.

A first difficulty is that these individual responses have complex (or even counteracting) effects on whole-plant performance. In general, reduction in leaf area and stomatal closure

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often are associated with a water conservation strategy but may cause a decrease in cumulated photosynthetic activity and therefore limit biomass production (Tardieu, 2012). In addition, reduction in cell division in leaves does not necessarily induce a reduction in leaf area, as a reduced number of cells might be compensated by an increase in cell size (Aguirrezabal et al., 2006).

Second, all of these responses and their effects on whole-plant performance depend upon the water deficit scenario itself (i.e., its severity, its duration, and its position during the life-cycle of the plant). For example, similar water deficit scenarios (i.e., with the same intensity and same duration) affect leaf growth more severely if imposed early during leaf development, while the cell cycle is still active within the leaf (Granier and Tardieu, 1999). Another example is found in maize (*Zea mays*), in which water deficit leads to the downregulation of photosynthesis genes during the vegetative growth phase and to a significant reduction in biomass production (Boyer and Westgate, 2004). Targeted approaches to increase drought tolerance in maize therefore have concentrated on vegetative parameters, particularly those associated with photosynthesis and stay-green phenotypes (Nelson et al., 2007; Lopes et al., 2011; Virloquet et al., 2011). However, water deficit during the flowering stage also leads to major reductions in yield due to reduced numbers of floral meristems and ovaries as well as increased kernel abortion (Boyer and Westgate, 2004). In conclusion, overall plant performance cannot be inferred from the plant growth response to drought at a single time point. Plant growth, including cell division and expansion processes, can recover when the soil water conditions become favorable again (Aguirrezabal et al., 2006; Lechner et al., 2008; Skirycz et al., 2011b).

Finally, while there is little evidence for a universal stress response, common stress responses appear to exist. Recent results even demonstrate that the regulation of stress responses is organized by specific tissues and cell types in the *Arabidopsis thaliana* root and that this process depends on developmental key regulators (Dinnyen et al., 2008; Iyer-Pascuzzi et al., 2011). For example, the key cell identity regulator SCARECROW binds to regulatory regions of stress-responsive genes (Iyer-Pascuzzi et al., 2011).

Therefore, adaptation for sustained production of biomass and seed yield under adverse water supply will remain a major challenge for crop improvement. Individual measures for improving drought tolerance must be evaluated carefully and on a case-by-case basis, rendering respective approaches very challenging but, nonetheless, essential.

CLASSICAL APPROACHES FOR TACKLING DROUGHT STRESS

The plant's transcriptional changes during drought stress have been extensively studied in a wide range of species, including *Arabidopsis* (Seki et al., 2001, 2002; Kilian et al., 2007; Huang et al., 2008; Matsui et al., 2008), oilseed rape (*Brassica napus*)

(Chen et al., 2010), rice (*Oryza sativa*) (Lenka et al., 2011; D. Wang et al., 2011), maize (Luo et al., 2010; Chen et al., 2011), loblolly pine (*Pinus taeda*) (Lorenz et al., 2011), and banana (*Musa* spp) (Davey et al., 2009). Analyses of gene expression, transcriptional regulation, and signal transduction in plants subjected to drought treatments have revealed pathways involved in plant response to water stress (Seki et al., 2001; Abe et al., 2003; Tran et al., 2004). Importantly, comparative analysis of some of these data sets indicates a high level of conservation in plant responses to drought stress (Davey et al., 2009). However, most analyses have been performed by imposing very severe water deprivation far away from the mild stress conditions that plants usually have to cope with in natural environments. In many experimental setups, plants were subjected to total water deprivation during long periods or aboveground parts were even separated from the root system to simulate drought (Iuchi et al., 2001; Kawaguchi et al., 2004; Hausmann et al., 2005).

Genes that are either induced or repressed during those treatments have been classified mainly into two groups. A first group is involved in cell-to-cell signaling and transcriptional control. It is well established that the phytohormone ABA serves as an endogenous messenger in drought stress responses of plants: Drought causes increases of ABA levels in plant leaves, with major changes in gene expression and physiological responses (Raghavendra et al., 2010). In this context, many efforts have focused on investigating signaling via ABA as the key regulator controlling yield under drought (Hirayama and Shinozaki, 2010; Skirycz et al., 2011b). Components of the second group have functions in membrane protection, including production of osmoprotectants and antioxidants as well as reactive oxygen species scavengers. All of these processes have been major targets of genetic engineering approaches to produce plants that have enhanced stress tolerance (Valliyodan and Nguyen, 2006; Trujillo et al., 2008; Goel et al., 2010; Quan et al., 2010; Manavalan et al., 2012).

It was demonstrated recently that even though engineered plants are more likely to survive extreme drought stress conditions (that are often imposed in laboratory experiments), they do not necessarily grow better under milder stress conditions (Skirycz et al., 2011b) or when multiple, simultaneous stresses would occur. This finding is relevant as drought is rarely severe enough to kill plants in an agricultural context but rather reduces plant growth. A major difference between severe and mild stresses is that plants limit their photosynthesis under severe stress conditions, and this resource limitation, in turn, affects growth. By contrast, plants reduce their growth during moderate drought without decelerating photosynthesis (reviewed in Muller et al., 2011).

An increase in stress tolerance is often aimed for by rather general approaches, namely, ectopic overexpression or knock-down of a particular key component of stress signaling pathways (Nelson et al., 2007; Xiao et al., 2007; Castiglioni et al., 2008; Jung et al., 2008; Li et al., 2011; Song et al., 2011; Yan

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et al., 2011). Ectopic expression of components involved in abiotic stress responses has led to improved stress tolerance, but also reduced plant growth (Flowers, 2004; Bartels and Sunkar, 2005; Umezawa et al., 2006). However, strategies to avoid collateral growth problems of broad overexpression, such as strong drought-inducible promoters or promoters with specific expression patterns, have been employed or proposed (Kasuga et al., 2004; Cominelli and Tonelli, 2010; J.S. Kim et al., 2011).

In addition, manipulation of genes that function in drought stress responses, such as changes in stomatal conductance and osmolyte production, have not yet resulted in significant crop improvement (Umezawa et al., 2006; Hirayama and Shinozaki, 2010; Skirycz et al., 2011b). Key reasons for this failure are genetic and physiological differences between model and crop species and indiscriminate selection for lines that survive better under severe stress (Seki et al., 2007; Skirycz et al., 2011b).

A NEW APPROACH: RLKs AND DROUGHT STRESS

An analysis of the AtGenExpress drought transcript profiling data set (Kilian et al., 2007) revealed that there were substantial changes occurring in *RLKs*, based on a list containing 610 family members by Shiu and Bleecker (2001a) (Figures 2 and 3). At the 1-h time point after onset of drought treatment, there was a peak in upregulated *RLK* genes showing that there is a rapid response to the initial drought treatment in root and shoot. This indicates that *RLKs* may be essential for a rapid drought response. Among upregulated *RLKs*, several genes were also among the 78 *RLKs* differentially expressed in proliferating leaf primordia microdissected from *Arabidopsis* seedlings subjected to mild osmotic stress (Skirycz et al., 2011a). This osmotic stress data set was particularly enriched in domain of unknown function 26 *RLKs*, also called cysteine-rich receptor-like kinases (*CRKs*), which have been suggested to play important roles in the regulation of pathogen defense and programmed cell death (Wrzaczek et al., 2010). However, the exact functions of the vast majority of the 78 *RLKs* are unknown. A remarkable exception is *PHYTOSULFOKIN RECEPTOR1*, a Leu-rich repeat (*LRR*) *RLK* mediating plant growth and differentiation by phytosulfokines (Kwezi et al., 2011). Interestingly, some of the identified *RLKs* were previously proposed to be salt stress resistant (ten Hove et al., 2011), and, since these abiotic stress responses have much in common (Munns, 2002; Bartels and Sunkar, 2005), these could provide a good starting point for drought stress studies (Figure 2).

Recently, a similar analysis of transcript profiling data led to the identification of *ABA- AND OSMOTIC STRESS-INDUCIBLE RECEPTOR-LIKE CYTOSOLIC KINASE1* (*ARCK1*) as a negative regulator of abiotic stress signal transduction (Tanaka et al., 2012). The analyses of an *arck1* mutant and *CRK36* RNA interference transgenic lines strongly suggests that modulating *RLKs* could have a clear impact on stress response and that the

formation of appropriate complexes, for instance, between *ARCK1* and *CRK36*, might be required to adjust plant growth in response to environmental conditions (Tanaka et al., 2012).

In general, *RLKs* are considered key regulators of plant architecture and growth behavior, and the dramatic expansion of this superfamily during the evolution of higher plants has also been correlated to species-specific adaptations in defense and stress responses (Lehti-Shiu et al., 2009). Therefore, *RLKs* provide unique opportunities for increasing drought resistance in plants. In particular, the vast number of *RLKs*, their involvement in specific signaling cascades, and their widespread dependence on small molecules might allow the highly controlled modulation of individual physiological processes in temporal and spatial terms.

RLKs and their associated endogenous peptide ligands are encoded by ~600 and ~1000 genes, respectively, in the *Arabidopsis* genome, and there are more in crops such as rice, maize, and oilseed rape (Shiu and Bleecker, 2001a, 2001b, 2003; Shiu et al., 2004; Lease and Walker, 2006; Butenko et al., 2009; Schnable et al., 2009). Whole-genome studies have further shown that genes encoding the largest *RLK* subfamily of *LRR* *RLKs* covary significantly between species in terms of numbers and structure and therefore have been predicted to possess similar functions (Hwang et al., 2011; J. Wang et al., 2011). Their evolutionary conservation therefore circumvents the problematic genetic differences between model and crop species and allows global extrapolation after *LRR* *RLK* studies have been performed in model plants (Shiu et al., 2004).

It has been shown in a number of studies that *RLKs* and their peptide ligands play key roles in regulating vegetative growth and development, protection against pathogens, and reproductive success in generating seeds and fruits and hindering premature abscission (Afzal et al., 2008; Sanabria et al., 2008; De Smet et al., 2009; Tör et al., 2009; Zhao et al., 2009; Aalen, 2011; Boisson-Demier et al., 2011; Gish and Clark, 2011; Nodine et al., 2011; Butenko and Aalen, 2012). The overall picture that emerges from many different studies is one of a bewilderingly complex set of *RLKs* that may be specific to the level of individual cells. One attractive hypothesis for the advantage of such a complex organization of receptors is that it would allow crosstalk at the level of perception. Indeed, regulation of distinct signaling pathways employs different receptor complex subsets, mediated by different ligand binding *RLKs* by an otherwise common regulatory *RLK*, and may rely on different phosphorylation patterns (Roux et al., 2011; Schwessinger et al., 2011; Albrecht et al., 2012). Given the fact that coordinated control between different cell populations is also required, it is proposed that an extensive network of receptors exist in largely independent and preformed complexes wired to various response machineries (Abrash et al., 2011; Albrecht et al., 2012).

There are several examples for central roles of *RLKs* and their respective peptide ligands in the control of developmental processes (Butenko et al., 2009; De Smet et al., 2009; Gish and Clark, 2011; Butenko and Aalen, 2012). Overall growth and

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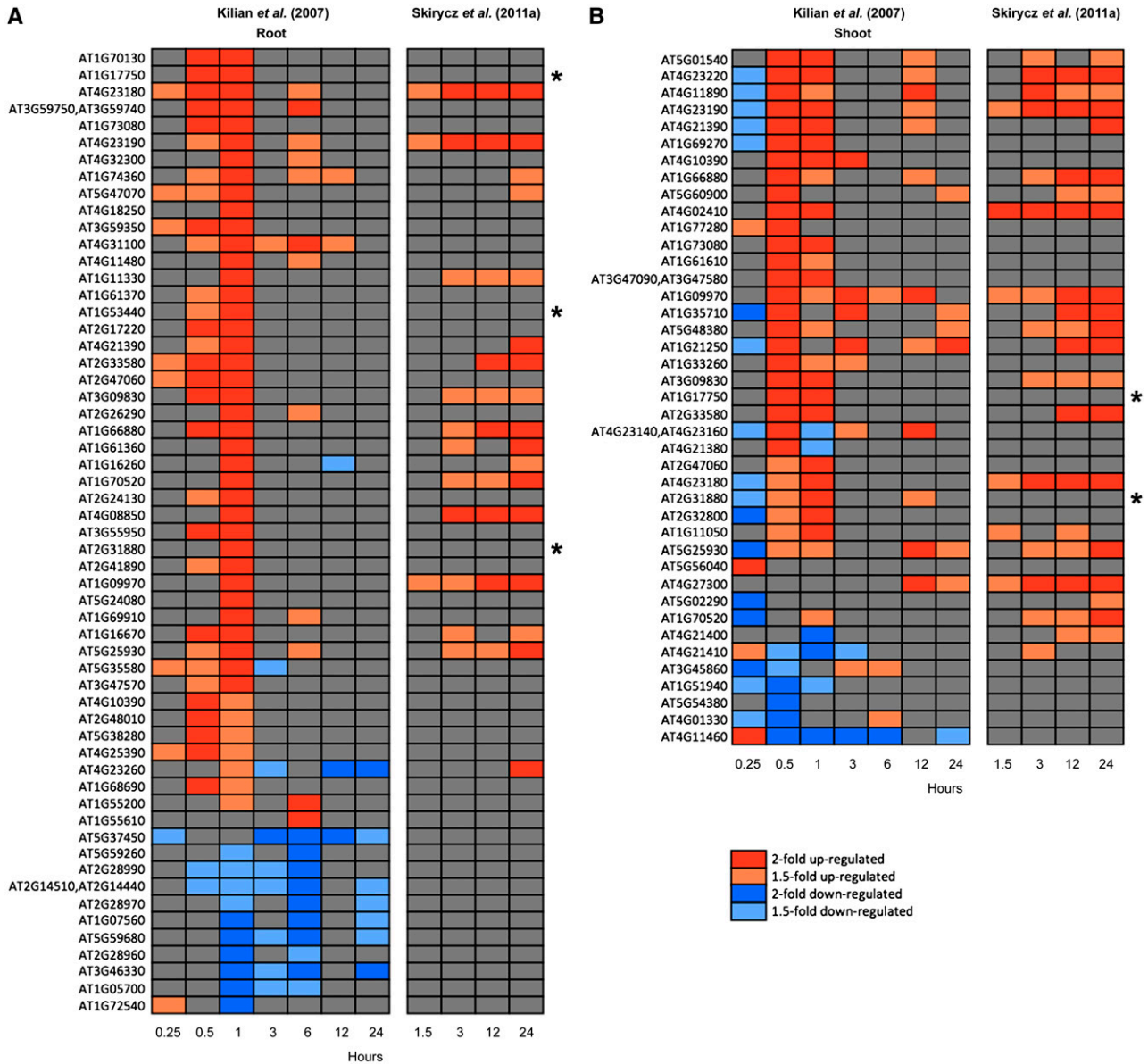


Figure 2. Screen for Differentially Expressed *RLK* Genes in *Arabidopsis*.

Data were taken from a drought stress time series across root (**A**) and shoot (**B**) tissues (AtGenExpress; Kilian et al., 2007). In addition, data from a mannitol treatment for corresponding *RLKs* is shown (Skirycz et al., 2011a). Kilian et al. (2007) applied drought stress as follows: The plants were exposed to a stream of air in a clean bench for 15 min, which resulted in a loss of 10% of the plant's fresh weight. Subsequently, plants were returned to the growth chamber and harvested at indicated time intervals. Skirycz et al. (2011a) used an experimental setup that reproducibly reduced the leaf area by ~50%. Seedlings 9 d after stratification were transferred to 25 mM mannitol-containing medium (decreasing the water potential of the medium and, hence, water uptake of the exposed roots), and leaf primordia were harvested at indicated time intervals. The AtGenExpress drought microarray data set (Kilian et al., 2007) was downloaded from NASCArrays (Craigon et al., 2004) and then RMA normalized and analyzed using Bioconductor (Gentleman et al., 2004), which generated log₂-fold changes across all of the probes. This list was filtered for 610 *RLK* family members (Shiu and Bleecker, 2001a). Blocks represent twofold upregulated (red), 1.5-fold upregulated (orange), twofold downregulated (blue), and 1.5-fold downregulated genes (light blue) in drought stress relative to control tissue. Asterisks indicate *RLKs* investigated by ten Hove et al. (2011), with T-DNA mutants displaying salt stress resistance.

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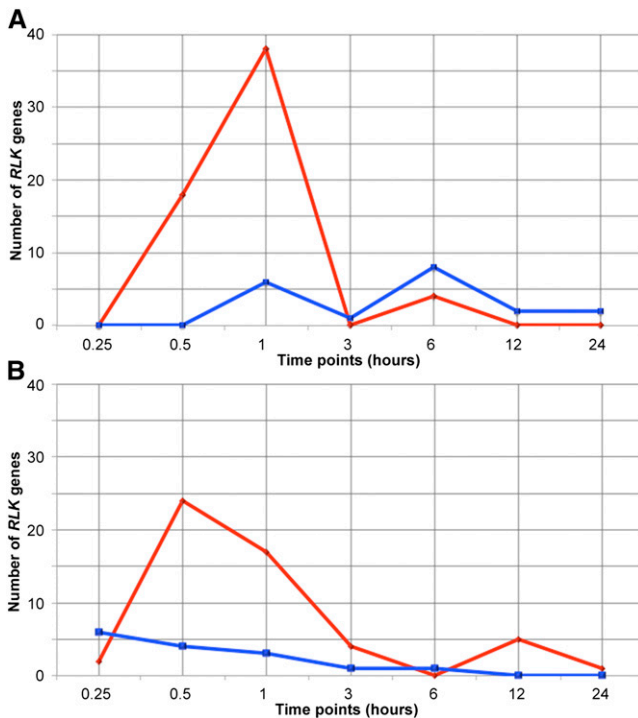


Figure 3. Early Effect of Drought on *RLK* Expression.

Number of *RLK* genes identified as candidates for differential expression within 24 h of onset of drought stress. Data from the AtGenExpress drought microarray data set (Kilian et al., 2007) at the time points 0.25 to 24 h for root (**A**) and shoot (**B**). Putative differential expression is defined as twofold or greater change in expression in drought stress relative to control tissue. Red and blue lines represent the number of upregulated and downregulated *RLK* genes, respectively. There is a large spike in upregulated gene numbers at the 1-h time point in the root and at the 0.5-h time point in shoot.

organ production, such as leaves or floral organs, depends on the plant's stem cell niches, the meristems. The stem cell pools in shoot and floral meristems of higher plants are controlled by a peptide ligand–RLK pathway, with a 13–amino acid CLAVATA3/EMBRYO SURROUNDING REGION-RELATED (CLE) peptide and CLAVATA1-type LRR RLK as key components, which provides a feedback signal from established stem cells to an organizer region, which in turn promotes stemness in meristems. Reducing the activity of the stemness-repressing CLAVATA pathway allows the formation of larger meristems, larger flowers, and often also larger fruits with the potential to generate more seeds (Bommert et al., 2005). A similar mechanism appears to exist in the root apical meristem, with CLE40 and ARABIDOPSIS CRINKLY4 as central players (De Smet et al., 2008; Stahl et al., 2009). Thus, RLK-dependent meristem regulation has the potential for serving as a target for uncoupling plant growth from general drought responses. Another example

is the patterning of the leaf epidermis and the generation of stomata, which is governed by LRR RLKs of the ERECTA family and EPIDERMAL PATTERNING FACTOR (EPF)–type peptide ligands. During early leaf stages, the Cys-rich EPF1 and EPF2 peptides are expressed in stomata precursors and repress stomata development in neighboring cells by binding and activating receptor complexes, consisting of ERECTA family RLKs and the receptor-like protein TOO MANY MOUTHS (Lee et al., 2012). These signaling systems allow the generation of stomata, fine-tuned to the specific requirements of different plant organs. The targeted modulation of stomatal density by RLK-based manipulation of these systems can be expected to have a positive impact on drought tolerance without significantly affecting the overall growth of the plant.

While the role of RLKs and peptide ligands in development and biotic stress responses is well documented, their direct involvement in abiotic stress resistance has only recently been suggested (Boller and Felix, 2009; de Lorenzo et al., 2009; Osakabe et al., 2010; Wrzaczek et al., 2010; ten Hove et al., 2011; Gao and Xue, 2012). Interestingly, many *RLK* genes that are expressed during late stages of seed development associated with embryo and endosperm dehydration are also regulated by abiotic stresses, including drought, indicating that RLK activities are involved in multiple signaling pathways associated with water deficit (Gao and Xue, 2012). Moreover, a number of RLKs have recently been shown to be regulated by drought, heat, and cold; many stress responses, including ABA signaling, are likely integrated by RLKs (Chae et al., 2009; de Lorenzo et al., 2009; Osakabe et al., 2010; Wrzaczek et al., 2010; Oh et al., 2011; ten Hove et al., 2011; Xing et al., 2011; Gao and Xue, 2012).

One of the best-characterized LRR RLKs in plants is BRASSINOSTEROID INSENSITIVE1 (BRI1), the receptor for brassinosteroid (BR) hormones (Li and Chory, 1997). BRI1 has an extracellular domain made of 24 LRR domains interrupted by a 70–amino acid island domain placed between the 20th and 21st LRR that creates a surface pocket for binding the plant hormone brassinolide, a transmembrane domain, a functional cytoplasm Ser/Thr kinase domain, a juxtamembrane domain, and a short C-terminal domain (Li and Chory, 1997; Friedrichsen et al., 2000; Wang et al., 2005; Hothorn et al., 2011). The presence of the island domain in the extracellular LRRs has served to identify three BRI1-like homologs in *Arabidopsis*, from which BRL1 and BRL3 are true BR receptors in the vasculature (Caño-Delgado et al., 2004). In the presence of brassinolide, BRI1 interacts with another LRR RLK protein, SOMATIC EMBRYOGENESIS RECEPTOR-LIKE KINASE3/BRI1-ASSOCIATED RECEPTOR KINASE, at the cell surface (Rusznova et al., 2004). This activates downstream signaling events that are transmitted to the nucleus through sequential signaling modules (Clouse, 2011). The transcriptional regulation of BR-responsive genes enables the plant to grow and adapt to internal cues and major environmental conditions, including tolerance to biotic and abiotic stresses (Gudesblat and Rusznova, 2011; Vriet et al., 2012). The

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dwarf size of *bri1* alleles is the result of impaired cell division and elongation in roots, shoots, and leaves (Gonzalez et al., 2010; González-García et al., 2011).

Whereas many studies demonstrate a positive effect of BR application on plant tolerance to salt and drought stresses in several plant species (Krishna, 2003; Bajguz and Hayat, 2009; Gomes, 2011), only a few have evaluated the effects of altered endogenous BR content or signaling on tolerance to these stresses. In *Arabidopsis*, a single amino acid replacement in BRI1 that eliminates a Tyr autophosphorylation site, which negatively regulates BRI1 activity, strongly promotes shoot growth, together with increased Pro production that is normally associated with water stress (Oh et al., 2011). The *bri3* mutants exhibit an increased osmotolerance in root growth assays, suggesting a role for the vascular BR receptor BRL3 in salt stress tolerance (ten Hove et al., 2011). In barley (*Hordeum vulgare*), the semidwarf *uzu* mutant that is defective in the Hv-BRI1 gene displayed reduced tolerance to this stress (Chono et al., 2003). Conversely, overexpression of the HYDROXYSTEROID DEHYDROGENASE1 gene that encodes a putative enzyme involved in BR synthesis in *Arabidopsis* increased tolerance to salt stress (Li et al., 2007). Similarly, seeds and seedlings of the *Arabidopsis* BR-deficient mutant *de-etiolated2* and the BR signaling mutant *brassinosteroid-insensitive2 (bin2)*, defective in the GSK3/Shaggy-like protein kinase BIN2, were more sensitive to salt stress than that of the wild type (Zeng et al., 2010). In agreement with this, the rice T-DNA knockout mutants of Os-GSK1, a BIN2 ortholog, displayed an increased tolerance to both salt and drought stresses (Koh et al., 2007).

Although the results described above point toward a clear effect of BRs on plant salt and drought stress tolerance, the molecular mechanisms involved in these processes remain largely unknown. BRs might affect plant drought tolerance by controlling the number of stomata, as the density or clustering of stomata per leaf area is increased in some *Arabidopsis* BR- and sterol-deficient mutants (Catterou et al., 2001; Schlüter et al., 2002). This modulation of stomatal density was recently further supported by the uncovering of molecular interactions between components of BRs and stomatal signaling pathways (Gudesblat et al., 2012; Kim et al., 2012). Another possible molecular mechanism that links BRs with abiotic stress tolerance involves regulated intramembrane proteolysis triggered by endoplasmic reticulum stress signaling. Stress-mediated increase in the translocation to the nucleus of two bZIP transcription factors associated with endoplasmic reticulum stress was found to activate BR signaling and was required for stress acclimation and growth (Che et al., 2010).

Apart from BRI1, various other RLKs have been implicated in drought responses in several plant species. In poplar (*Populus* spp), short periods of water shortage induced expression of a specific RLK in wood-forming tissue (Berta et al., 2010). In addition, water use efficiency was improved by the expression of a poplar ortholog of *ERECTA* in *Arabidopsis* (Xing et al., 2011). A biochemical explanation for this effect of Pd-*ERECTA* is still

missing, but the reduction in stomatal density controlled by *ERECTA* is expected to contribute to a decreased transpiration rate and higher water use efficiency. Recently, it was also shown that overexpression of the LRR RLK Os-*SIK1* that affects stomatal density in the leaf epidermis of rice leads to higher tolerance to salt and drought stresses. On the contrary, *sik1* knockout mutants as well as *SIK1* RNA interference plants are sensitive to drought and salt stresses (Ouyang et al., 2010). A network of positive and negative RLK peptide ligands has been identified in the leaf epidermis modulating RLK activity and, thus, stomata density and drought stress tolerance (Shimada et al., 2011). These examples further show that developmental and stress responses are interrelated in plants via signal integration involving RLKs.

Interestingly, plant early responses to drought and salt stress are largely identical, but it is only after several days that salt-specific effects start to have an impact on growth (Munns, 2002; Bartels and Sunkar, 2005). Indeed, a large overlap in gene expression was observed in plants exposed to drought or salt stress (Seki et al., 2002; Chen et al., 2010). Similarly, the high regulatory consistency by both salt and drought of RLK genes suggests a close relationship between these two response pathways and RLKs' effects in the response to salt and drought (Gao and Xue, 2012). Screening mutants for a set of 69 root-expressed LRR RLKs with respect to effects of salt stress on root growth revealed 23 genes playing a potential role in salt tolerance (ten Hove et al., 2011). However, no clear relationship between the identified RLKs and their phylogeny was detected (ten Hove et al., 2011) suggesting that RLKs readily acquire different functions compared with their closest paralogs. It was found that a LRR RLK gene, *SRLK*, from the legume *Medicago truncatula* was rapidly induced by salt stress in epidermal root tissues. Accordingly, *srlk* mutants failed to limit root growth in response to salt stress (de Lorenzo et al., 2009). A signal transduction pathway mediated by *SRLK* was linked to the activation of a member of the calcium-dependent protein kinase (CDPK) gene family (de Lorenzo et al., 2009), which is often linked to adaptation responses to biotic and abiotic stresses (Das and Pandey, 2010).

TRANSLATIONAL APPROACHES: FROM MODEL TO CROP

So far, successful transfer of new technologies from model systems to crop plants has often been hampered by genetic and physiological differences between species (Skirycz et al., 2011b). In this respect, orthologous peptide ligand and RLK genes have been identified in *Arabidopsis*, oilseed rape, maize, and rice, revealing a high level of sequence conservation, even comparing monocot and dicot plants (Schnable et al., 2009; X. Wang et al., 2011; Gao and Xue, 2012). Examples for functional similarity are CLAVATA-like RLKs, which restrict meristem activity in both *Arabidopsis* and rice (Suzaki et al., 2009), and CRINKLY4-like RLKs that control epidermal cell differentiation in

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Arabidopsis, maize, and rice (Becraft et al., 1996; Watanabe et al., 2004; Pu et al., 2012). This strongly supports the notion that peptide ligands and RLKs are evolutionarily highly conserved, thereby offering the potential to circumvent problematic genetic differences between model and crop species (Shiu et al., 2004) and allowing chemical genetics approaches (see below).

In the context of drought stress, altering *RLK* expression levels has been shown to affect drought stress tolerance in crops (see above), and there are a number of (economically valuable) plant species that are excellent systems for further exploration of the role of RLKs under drought stress conditions, such as oilseed rape and maize. By contrast, the grass model species *Brachypodium* has not yet been characterized for its drought tolerance, and the well-studied (deepwater) rice grown in flooded conditions cannot serve as model to investigate drought tolerance.

The genus *Brassica* includes the closest crop relatives of *Arabidopsis*, making it an ideal model in which to study the role of RLKs in crop plants. This genus includes species such as the diploid *Brassica rapa* (A-genome, $2n = 2x = 20$), which includes vegetable (e.g., turnip and Chinese cabbage) and oilseed crops; *Brassica oleracea* (C-genome, $2n = 2x = 18$), which includes vegetable crops (e.g., cauliflower, broccoli, and cabbage); and the amphidiploid *B. napus* (AC-genome, $2n = 4x = 38$), which includes oilseed crops (e.g., canola and oilseed rape) and swede. As with many crop plants *Brassica* genomes are complex, arising from a series of duplication events that has resulted in most genes being present in multiple paralogous and homologous copies (Rana et al., 2004; Parkin et al., 2005). However, the recently published genome sequence of *B. rapa* should facilitate the identification of the genes encoding paralogous RLKs and potentially associated ligand candidates in *Brassica* species (X. Wang et al., 2011). These sequences can be used to identify an allelic series of mutations in target genes using TILLING populations that have been generated in both *B. rapa* (Stephenson et al., 2010) and *B. napus* (Wang et al., 2008), in conjunction with high-resolution melt analysis (Lochlainn et al., 2011). Sequence alignments of genes encoding potential peptide ligands implicated in abscission in *Arabidopsis* show a high degree of conservation also in the promoter region of their *B. rapa* homologs (L. Østergaard, M.A. Butenko, and R.B. Aalen, unpublished results), suggesting that the regulation of peptide ligand expression is conserved as well. This opens the possibility of manipulating conserved regulatory elements to fine-tune developmental processes involved in maintaining high yield under water stress conditions.

The monocotyledonous model crop plant maize (*Z. mays* subsp *mays*) was domesticated in Central America from *Balsas teosinte* (*Z. mays* subsp *parviglumis*) between 7000 and 9000 years ago (Matsuoka et al., 2002). Domestication and extensive breeding resulted in a large variety of landraces that were dispersed throughout the Americas and that are adapted to a wide range of environmental conditions capable of growing at various altitudes as well as in tropical, subtropical, and temperate

climates (Bush et al., 1989; Hayano-Kanashiro et al., 2009). At the beginning of the 20th century, a limited number of landraces were selected by plant breeders to generate the inbred lines that are used today in hybrid seed production. Thus, both domestication and crop improvement involved selection of genes controlling key morphological and agronomic traits with a major focus on grain yield. This went in parallel with reduced genetic diversity relative to unselected genes (Yamasaki et al., 2005). Those genes that underwent the most stringent selection have little remaining genetic variation and cannot easily be further improved by conventional plant breeding. Moreover, many genes and traits were lost from germplasm of modern inbred lines, such as nutritional quality determinants and stress tolerance (Swarup et al., 1995). By contrast, many maize landraces are tolerant to water deficit and other stresses (Hayano-Kanashiro et al., 2009). Due to global climate change and limited water resources, development of drought stress-tolerant maize cultivars is one of the primary goals of today's plant breeding programs. Maize belongs to the crops that have been adapted to the widest range of environmental conditions (Hayano-Kanashiro et al., 2009). Its allo-tetraploid genome has undergone several rounds of genome duplication beginning with a paleopolyploid ancestor ~70 million years ago (Paterson et al., 2004) and an additional whole-genome duplication event ~5 to 12 million years ago (Swigonova et al., 2004). The large range of wild varieties and landraces adapted to various stress conditions still provide an excellent resource for further genetic improvements of cultivated maize (Vielle-Calzada et al., 2009). Given the economic importance of grass crops, it is tempting to introduce valuable genomic traits from less related species and even dicotyledonous plants. However, due to the often sparse synteny between dicots and monocots, this approach might meet problems of genetic incompatibility (Spannagl et al., 2011), but peptide ligands and RLKs are evolutionarily highly conserved, thereby circumventing these problems (Shiu et al., 2004).

A CHEMICAL APPROACH: THE VALUE OF SYNTHETIC REGULATORY MOLECULES

It can be expected that synthetic molecules that activate or repress regulatory proteins such as RLKs could provide powerful chemical tools to interfere with the corresponding signaling pathways. Unlike genetic approaches, in which mutations are introduced at the DNA level to permanently perturb gene expression or function, synthetic molecules exert their effects directly and immediately at the protein level. This mode of interference with biological processes brings along important advantages. First, such interference using regulatory molecules should be applicable to proteins that are not amenable to genetic analysis, including RLKs. For example, particular RLKs may have an indispensable role in an early stage of development or be important for adaptive processes in later phases of the life cycle of the plant. Synthetic molecules affecting RLKs can be added and assessed for their function at any stage of

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development. Also, synthetic molecules can target conserved sites on related proteins encoded by multiple gene copies and thus overcome problems of redundancy often encountered with genetic approaches. With respect to translational research, the application of synthetic molecules is promising as well because, due to evolutionary conservation of the regulatory systems, synthetic molecules that function in model species are likely to be effective in other plants as well.

A prerequisite to finding new chemicals that interfere with a certain biological pathway or a protein of interest is the availability of a chemical genetic toolbox, including a large collection of compounds that are capable of altering the function of particular proteins in specific biological processes. The screening collection might consist of synthetic molecules, natural products, or peptide ligands. A collection of synthetic molecules can be diverse if no prior knowledge of the protein target is known and the screening aims at the identification of compounds that interfere with a biological pathway rather than a specific protein. On the other hand, if structural information is known about the protein site(s) to target, then a more focused library can be used in which screening compounds (synthetic molecules or peptides) are synthesized based on one or several structural scaffolds. To assess the potential effect of a compound collection on a particular biological process or protein of interest, a robust screening assay must be developed in a model system, which can include cell-free or cellular systems or even small model organisms such as *Arabidopsis* seedlings in 96- or 384-well plates. After assay development and acquisition/synthesis of the screening compounds, the compound collection is applied to the assay system in a high-throughput fashion using automated liquid handling platforms and the assay output is detected by means of automated plate readers or microscopes. After hit identification, hits are validated with secondary screening assays and chemical characterization, including evaluation of chemical structure and initial structure-activity analysis. Recently, chemical genetics has been successfully used to investigate signaling pathways and to modulate plant growth (Hayashi et al., 2008; Savaldi-Goldstein et al., 2008; De Rybel et al., 2009; Tsuchiya et al., 2010; T.H. Kim et al., 2011).

For example, the identification of the synthetic molecule pyrabactin (4-bromo-*N*-[pyridin-2-yl methyl]naphthalene-1-sulfonamide) as a selective ABA agonist has led to major breakthroughs in ABA perception mechanisms. Although many intermediate signaling components had been described previously, knowledge at the level of ABA perception was only marginal (Finkelstein et al., 2002). Progress via genetic approaches was hampered by the high genetic redundancy of the ABA receptor gene family. However, this redundancy effectively was bypassed by the selectivity of pyrabactin for a subset of ABA receptors and led to the identification of PYRABACTIN RESISTANCE (PYR)/REGULATORY COMPONENT OF ABA RECEPTOR (RCAR) proteins as ABA receptors (Park et al., 2009). The PYR/RCAR proteins act together with PP2Cs and SnRK2s as negative and positive regulators respectively of

downstream ABA signaling (Ma et al., 2009; Park et al., 2009). This breakthrough, together with further detailed structural and mutational approaches, provided new insights into ABA perception and signaling (Melcher et al., 2010; Mosquna et al., 2011).

In addition to specific agonists, such as pyrabactin, general antagonists can also be powerful chemical tools. For example, bikinin was identified as an activator of BR signaling in a screen for small molecules that induce a constitutive BR response (De Rybel et al., 2009). Detailed mechanistic studies demonstrated that bikinin acts as an inhibitor of GLYCOGEN SYNTHASE KINASE3 (GSK3) kinases. In *Arabidopsis*, a set of 10 GSK3 kinases is present (Jonak and Hirt, 2002). Interestingly, because bikinin targets several subsets of GSK3 kinases, including a subset of three GSK3 kinases shown to be involved in the negative regulation of BRs signaling, the compound could act as a conditional and multiple knockout tool for this subset of GSK3 kinases and therefore induce a BRs response (De Rybel et al., 2009; Gudesblat et al., 2012; Kim et al., 2012). This type of response would not have been observed by single loss-of-function mutants in genes encoding GSK3 kinases or by a selective GSK3 kinase inhibitor.

However, there are only few small molecules known thus far that efficiently and specifically modulate plant signaling cascades. This may in part be due to the fact that many plant signaling pathways are initiated by protein-protein interactions, for example, as recently defined for auxin (Tan et al., 2007), gibberellic acid (Murase et al., 2008), ABA (Ma et al., 2009; Park et al., 2009), and BR (Hothorn et al., 2011; She et al., 2011) hormone sensing. The development of small molecules that can modulate such protein-protein interactions will provide a challenge for future research. Screening systems suitable for high throughput will be a prerequisite to test chemical libraries. Establishment of such screening systems will depend on physiological, biochemical, and biophysical knowledge of the respective target interactions (Arkin and Wells, 2004). Such knowledge remains scarce in plant biology, but RLKs are an ideal target for this. To develop small molecule modulators of plant RLK signaling, it will be of prime importance to match ligands and receptors and to understand better at the mechanistic level how receptors bind their ligands and activate cytoplasmic signaling components.

The above examples illustrate the power of chemical genetics to identify chemical probes that can be applied to study biological processes. But also from a translational point of view small molecules could be of great value (i.e., by forming the starting point in the discovery of new agrochemicals). Evidently, this requires that the compound's target protein(s) and/or the mechanism of action are conserved between the species in which the activity of the compound was observed (e.g., *Arabidopsis*) and the target crop species. In addition, based upon analysis of currently available pesticides and herbicides, agrochemicals obey certain structural and physico-chemical rules (Tice, 2001). The ranges of parameters for agrochemicals are

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similar to drug-like properties (Lipinski et al., 2001), except for the lower acceptable number of H-bond donors. However, some important differences exist between agrochemicals and pharmaceuticals regarding the types of functional groups (Tice, 2001). For example, for effective crop protection, a chemical must persist in the field for several weeks to be of practical value. Therefore, alcohols and amines are much less common in agrochemicals than in pharmaceuticals as these groups are less stable in field environments (due to ease of oxidation). Aromatic rings are also more prevalent among agrochemicals because they are more likely to be stable in the environment than alicyclic rings. Finally, acidic groups such as carboxylic acids and acylsulfonamides are prevalent among postemergence agrochemicals. This is because weakly acidic groups promote phloem mobility, which is required to transport the chemical to the growing points of the plant. These structural, functional, and physico-chemical constraints should be considered during the assembly of a compound screening collection with the aim to identify new types of agrochemicals.

FUTURE PERSPECTIVES AND CONCLUSIONS

From the available literature and our own analyses it is clear that RLKs can and will play a crucial role in tackling drought stress. In particular, since RLKs are evolutionarily conserved and often act at a level that is focused on a specific (cell- or tissue-specific) process, altering their activity will overcome some of the current difficulties. It is also likely that the solutions offered here can be applied to water stress in a broader sense, along with associated stresses, such as high salinity or freezing.

To achieve this, a systems biology approach is required to understand stress response and make use of available tools for high-spatial and temporal resolution analysis (Wee and Dinneny, 2010). The use of network analyses and mathematical modeling has already been put forward with respect to understanding drought stress (Tardieu et al., 2011; Tardieu, 2012). Network biology is one of the most effective approaches to manage large amounts of information through visual frameworks representing the complexity of the data as it offers great flexibility, which can include (predicted) protein interactions, coexpression, metabolism, and cell-to-cell signaling into the same graphic network structure (Stark et al., 2006; Geisler-Lee et al., 2007; Obayashi et al., 2007; Cui et al., 2008; Brandão et al., 2009; Hubbard et al., 2009; Aranda et al., 2010; Arabidopsis Interactome Mapping Consortium, 2011; Lin et al., 2011; Kerrien et al., 2012). The network approach may greatly enhance the understanding of the way genes and proteins interact. Furthermore, additional data can be mapped onto the network including metabolism, cell-to-cell signaling, RNA-Seq data, and literature-confirmed findings. However, as *Arabidopsis* network data increase and more closely represent biology, more effective database storage solutions and analytical scripts will be required to comb through the huge amount of data. Detailed analysis of available data sets, including gene network analysis, should provide insights into the key regulators of drought stress responses, and already

has identified several RLKs (Figures 2 and 3). The resulting drought networks can then be compared with other stresses and should allow the identification of drought-specific regulators. Ultimately, RLK signaling influences cellular changes, not in the least through transcriptional changes (De Smet et al., 2009). Therefore, network analyses and systems biology will provide insight on how to tie RLK research to other molecular components, such as transcriptional regulators, to provide an integrated solution to the drought stress problem. Future directions also include mathematical and dynamic modeling of the core drought network that will assist in identifying key regulators and downstream targets, guiding future mechanistic studies and ultimately translation to crop species.

We and others recently highlighted the importance of the root system in supporting a new green revolution (Lynch, 2007; Den Herder et al., 2010; De Smet et al., 2012). Stress signal transduction mechanisms from the perceptive tissues (mainly leaves) to the root system and to developing reproductive structures are now increasingly considered as main targets for yield improvement in crop plants under drought stress (Lopes et al., 2011). In this respect, further exploration of peptide ligands and RLKs involved in the regulation of root growth and development will be critical (De Smet et al., 2008; Stahl et al., 2009; Jun et al., 2010; Kinoshita et al., 2010; Matsuzaki et al., 2010; Meng et al., 2012).

Large numbers of signaling genes are regulated by drought stress in, for example, maize (Luo et al., 2010; Chen et al., 2011), but approaches to modify their activities in maize and other crops remain scarce. Furthermore, most of the genetically modified lines that have been developed to better withstand drought and other stress conditions have yet to be tested in the field (Tognetti et al., 2006; Nelson et al., 2007; Vanderauwera et al., 2007; Castiglioni et al., 2008). Modifying RLK growth regulators may positively contribute to biomass production by enhancing and modulating, for example, cell division and stomatal patterning, and at the same time render plants more tolerant against drought stress. Highly targeted and sophisticated approaches must be conducted to make plants more drought resistant and, at the same time, maintain growth rates. Ideally, these approaches should be effective in a large repertoire of species, meaning that underlying genes must be conserved. While further work is required for understanding how RLKs are mechanistically linked to drought stress responses, manipulation of RLK signaling is a promising approach for improving drought resistance in crops. There are numerous promising strategies that might fulfill these requirements, but, taken together, RLK signaling provides a means, together with other molecular processes, to meet the drought stress challenge.

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