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4 **AUTHORS:** Aditi Gupta, Andrés Rico-Medina, and Ana I. Caño-Delgado[*,]

5 **ADDRESS:** Department of Molecular Genetics, Centre for Research in Agricultural Genomics

6 (CRAG) CSIC-IRTA-UAB-UB, Campus UAB (Cerdanyola del Vallès), 08193 Barcelona, Spain.

7 *Corresponding author email: ana.cano@cragenomica.es

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13 **ABSTRACT**

14 Drought alone causes more yield loss annually than all pathogens combined (*1*). To adapt to

15 moisture gradients in soil, plants alter their physiology, modify root growth and architecture, and

16 close stomata on the above-ground plant. These tissue-specific responses modify the flux of signals

17 along the plant, resulting in early flowering or stunted plant growth that often reduce yield.

18 Physiological and molecular analyses of the model plant *Arabidopsis thaliana* (Arabidopsis) have

19 identified phytohormone signaling as key for regulating response to drought or water insufficiency.

20 Here, we discuss how engineering hormone signaling in specific cells and cellular domains

21 promises to improve plant responses to drought. We explore current knowledge and future

22 questions in the quest to produce high-yield, drought-resistant crops.

23

24

INTRODUCTION

Drought is a misfortune for agriculture, humanity and livestock alike. Climate change is leading us towards a hotter, more parched world (*2*). There is an urgent need to produce high-yielding plants that are more efficient at using water (Fig. 1a). In the last decade, global losses in crop production due to drought estimated around 30 billion dollars. Global population raised from 5 billion inhabitants in the 1990 to over 7.5 billion presently and is predicted to raise to 9.7-10 billion by 2050 (*3*), half of which (i.e. 5 billion people) is estimated to be living in water-scarce areas of the planet (Fig. 1b) (4). Despite the moderate increase is global arable land, an additional 1 million Ha will be needed to ensure food security (Fig. 1c) (5). In addition, water demand for agriculture need to duplicate by 2050, whereas the fresh water availability is predicted to drop by half cause of climate change (Fig. 1d) (6). Certainly, plant biotechnology holds one of the promises to meet the societal demand to duplicate crop production in the planet.

Water is crucial for plant survival and water deficit limits plant growth. However, plants have strategies to prevent water loss, to balance optimal water supply to all vital organs, to maintain the cellular water content, and to persevere through periods of drought. The ability of a plant to sense the water deficiency signal and initiate the coping strategies in response to drought signal is defined as drought resistance. Drought resistance is a complex trait that impinges on several mechanisms referred as: i) escape (acceleration of plant reproductive phase before stress that could hinder its survival), ii) avoidance (endurance with increased internal water content and preventing tissue damage), and iii) tolerance (endurance with low internal water content, whereas sustaining growth over the drought period (*7*). The percentage of viable plants after a period of drought upon re-watering is referred as drought survival. From molecular biology perspective, cellular water loss

48   marks the first event of drought stress. At the cellular level, drought signals promote production

49   of stress-protectant metabolites such as proline and trehalose; trigger antioxidant system to

50   maintain redox homeostasis and prevent acute cellular damage and membrane integrity by

51   peroxidase enzymes. Factors such as extent of water stress and the plant organ in which the stress

52   is sensed also trigger specific signaling responses, including but not limited to; abscisic acid,

53   brassinosteroids, and ethylene phytohormone pathways (*8-11*).

54

55   The impact that drought has on agriculture depends on the degree and duration of the reduced

56   precipitation and soil water gradients as well as on the species and developmental stage of the

57   plants (*8*). However, for most instances, crops experience moderate droughts caused by prolonged

58   precipitation deficits, reduced ground water levels, and/or limitation in accessing water supplies

59   leading to substantial losses in overall yield. Therefore, investigating the mechanisms of how a

60   plant sustains its growth during moderate drought and devising new strategies to improve plant

61   health during such moderate drought periods can provide us solution for future food security.

62   Understanding the response of cellular signaling to water shortage is a priority to answer the above-

63   mentioned questions for modern agriculture (*12*). Here we explore how water availability cues cell

64   and tissue growth patterns and how these growth patterns are coordinated in the whole plant to

65   improve drought resistance   without loss of yield. Overexpression of drought-responsive genes

66   often results in growth deficits and yield loss. Tissue- or time-specific expression of drought-

67   response traits may improve drought response without depressing yield. A combination of

68   strategies may improve agricultural yields despite increased water insecurity.

69

70   ***Traits for improving drought resistance***

71 During drought spells, plant systems work actively to maintain the physiological water balance.

72 This is achieved by: i) increased root water uptake from the soil, ii) reduced water loss by closing

73 stomata, and iii) osmotic adjustment within plant tissues (*13*). Activated stress response pathways

74 include phytohormone signaling, antioxidant and metabolite production and mobilization (*11*).

75

76 Roots respond to changes in soil moisture both at the cellular scale and at the entire root system

77 architecture. The root stem cell niche, meristem, and vasculature each coordinate responses for

78 drought (Fig. 2a, b). During water scarcity, the root system architecture undergoes morphological

79 changes to enhance its ability to absorb both water and nutrients (*9,10*). These modifications can

80 be traced to coordinated cell division, elongation and differentiation events in the root apex. Root

81 systems grow differentially to adapt their architecture to be either deep or shallow, in search of

82 moisture (Fig. 2c). Longer and deeper roots with reduced branching angles can efficiently capture

83 water from soil that may be dry at the surface but have deep layers retaining moisture. In contrast,

84 shallower root architectures are more beneficial in regions of low precipitations to maximize water

85 capture from the soil surface (*9*). Roots that encounter a soil environment with non-homogeneous

86 water distribution display hydro-patterning by favoring lateral root emergence towards soil patches

87 with higher water content, a process that is also mediated by auxin signaling (*9, 14*). Another

88 adaptive response to non-homogeneous distribution of moisture through soil is hydrotropism (Fig.

89 2d), where root tips grow towards zones with higher water content to optimize the root system

90 architecture for water acquisition (*15*).

91

92 Stomatal closure is a more rapid defense against dehydration (Fig. 2d, e). Stomatal pores, on leaf

93 surfaces, open or close according to turgidity of the surrounding guard cells. The turgor-driven

94 shape changes of guard cells are affected by cell wall structure, the plasma membrane, the

95 tonoplast properties, and cytoskeletal dynamics (*16*). Plant vascular tissues, xylem and phloem,

96 transmit water availability signals from roots to shoots and transmit photoassimilates from shoots

97 to roots respectively (*17*). Development of these inner vasculature tissues also affects drought

98 resistance. Crop yield becomes most vulnerable if the drought occurs during reproductive phase

99 of plant. In Arabidopsis, early flowering associated to drought escape is linked with the phloem

100 loading and transport of photoperiod-dependent protein FLOWERING LOCUS T (FT) from

101 leaves to the shoot apical meristem. (*18*)

102

103 *Phytohormones to combat drought*

104 The hormone abscisic acid (ABA) regulates plant responses to dehydration and optimizes water

105 use. Dehydration signals stimulate local production of ABA in different plant organs. However,

106 the ABA production is found to be most efficient in the leaf mesophyll cells compared to the root

107 tissues (*19*). The accumulated ABA then activates downstream signaling components (*20*). ABA

108 executes its function during stress by signal cross-talk with other pathways (Fig. 3) (*21*). Many

109 existing schemes to improve water use efficiency and drought resistance engage the ABA pathway.

110

111 Genetic engineering to improve Pyrabactin Resistance 1/PYR1-Like/Regulatory Component of

112 ABA Receptors (PYR/PYL/RCAR) and SnRK2s functions and repress the negative regulators

113 clade A type 2C protein phosphatases (PP2Cs) have resulted in improved water use efficiency in

114 plants such as Arabidopsis and wheat under controlled laboratory growth conditions and

115 glasshouses (*22-25*). A regulatory network of ABA pathway genes, a hierarchy of ABA-related

116 transcription factors, and signaling feedback were identified among ABA-mediated stress

117   responses to drought (*26*). Engineering the ABA receptor PYR1 for heightened sensitivity towards

118   the pre-existing agrochemical mandipropamid resulted in improved drought resistance in

119   Arabidopsis and tomato (*22*). Virtual screening for ABA receptor agonists led to the identification

120   of a bioactive ABA mimic called opabactin. This small molecule can enhance ABA receptor

121   activation and downstream signaling to improve water use efficiency and drought resistance in

122   Arabidopsis, tomato and wheat (*27*). Thus computational design combined with experimental

123   biology led to identify a small molecule that can mitigate the effects of drought on crop yields.

124

125   Brassinosteroid hormones also regulate drought response through signaling components linked to

126   the ABA response pathway (Fig. 3) (*28, 29*). Brassinosteroid signaling negative regulator

127   BRASSINOSTEROID-INSENSITIVE 2 (BIN2) is dephosphorylated by ABA INSENSITIVE1

128   (ABI1) and ABI2. ABA activates BIN2 by inhibiting ABI1/ABI2 activity (*30*). BIN2

129   phosphorylates SnRK2s and activates the downstream pathway (*31*). ABA signals can also

130   converge with the brassinosteroid pathway at the level of downstream transcription factors (Fig.

131   3). BRI1-EMS-SUPPRESSOR 1 (BES1) inhibited ABA induction of a drought-related

132   transcription factor RESPONSIVE TO DESICCATION 26 (RD26) (*32*). RD26 shows reciprocal

133   antagonism with brassinosteroid by modulating BES1-regulated transcription and inhibiting

134   brassinosteroid -regulated growth (*33*). WRKY46, 54, and 70 belong to another class of

135   transcription factors that interact with BES1 to promote plant growth while repressing drought

136   responses (*34*). BIN2 can phosphorylate and destabilize WRKY54 to negatively regulate its effect

137   on the BES1-mediated brassinosteroid response (*35*). BIN2 phosphorylates and activates the

138   ubiquitin receptor protein DSK2, which leads to BES1 degradation via autophagy and coordinates

139   plant growth and survival under drought conditions. (*36*). An AP2/ERF transcription factor called

140   TINY is another candidate that balances brassinosteroid-mediated stress adaptation with growth.

141   TINY interacts with BES1 and antagonizes brassinosteroid-regulated growth. BIN2 on the other

142   hand phosphorylates and stabilizes TINY to promote ABA-induced stomatal closure and drought

143   resistance (*37*). Thus, brassinosteroid as well as ABA aids drought resistance.

144

145   *Tissue-specific responses for drought resistance*

146   Stomatal closure preserves water in the plant. ABA content in leaves regulates stomatal movement

147   in response to water availability (*25*) (Fig. 3). Since stomatal movements control CO_2 influx and

148   transpiration, efforts to reduce water loss via stomatal closure occur at the cost of photosynthesis,

149   growth, and yield (*13*). Therefore, most strategies to improve water efficiency and drought

150   resistance in plants focus on fine-tuning stomatal conductance and manipulating ABA signaling

151   via stomata-specific promoters (*38*). With optogenetics, scientists have improved the

152   responsiveness of the stomata and overcome the coupling of CO_2 uptake with water vapor loss.

153   Upon introducing BLINK1, a light-activated synthetic K^+ ion channel, into guard cells, stomata

154   became more synchronized with fluctuating light conditions (*39*). This manipulation improved the

155   performance of the stomata and, as a consequence, growth and productivity of the plant. Thus,

156   water use efficiency was improved by engineering stomata to maximize the amount of carbon

157   fixed per unit of water lost.

158

159   Improving water acquisition by roots can also improve plant performance upon drought. In

160   Arabidopsis, an auxin pathway modulator EXOCYST SUBUNIT EXO70 FAMILY PROTEIN A3

161   (EXO70A3) that regulates depth of the root system was identified using a genome-wide

162   association (GWA) mapping (*40*). EXO70A3, a component of the exocytosis system, is expressed

163   in root tips. EXO70A3 regulates local auxin transport by affecting the homeostasis of auxin efflux

164   carrier PIN-FORMED 4 in root columella cells (Fig. 3). Natural variation in EXO70A3 was

165   correlated with seasonal precipitation and conferred different adaptive root system architecture

166   configurations under different rainfall patterns. In areas with high temperatures and irrigated soils,

167   deeper root architectures proved better for drought adaptation. In rice, an auxin inducible gene

168   *DEEPER ROOTING1* provides drought resistance by promoting a more vertical and deeper root

169   system architecture (*41*). Although auxin modulates root architecture under stress (*40, 41*),

170   hydrotropic root responses are fairly auxin-independent and involve ABA signaling in root

171   elongation zones. Coordinated activity of the ABA inducible MIZU-KUSSEI1 (MIZ1) and SNF1-

172   RELATED KINASE 2 (SnRK2.2), in root elongation zone cortical cells interprets water potential

173   gradients in soil environments (*15, 42*).

174

175   Brassinosteroid receptors regulate root hydrotropic responses (Fig. 3). Overexpression of a

176   vascular-enriched brassinosteroid receptor BRI1-Like3 (BRL3) promoted root hydrotropic

177   bending. The *brl1brl3bak1* triple mutant of BRL3 signalosome showed reduced hydrotropic

178   response, suggesting a role for the vascular BRL3 receptor complex in regulating hydrotropic

179   responses (*43*) (Fig. 3). Activation of the BRL3 pathway in vasculature triggered accumulation of

180   osmoprotectant metabolites such as proline, trehalose, and raffinose family oligosaccharides in

181   plant roots in response to water withdrawal, which improved drought resistance without penalizing

182   growth (*43*) (Fig. 3). Phloem-specific localization of BRL3 is likely to be the determining factor

183   for promoting drought resistance without impairing yield (*29, 43*).

184

185   In drought, roots sense water scarcity from soil. The above-ground plant responds by closing

186   stomata in leaves, thus implicating a systemic communication system. Upon drought, the CLE25

187   peptide is produced in the roots and moves through the vasculature to plant leaves to drive ABA

188   production by activating the biosynthetic enzyme NCED3. This burst of ABA synthesis leads to

189   stomatal closure and improved water balance, thereby promoting drought survival (*44*) (Fig. 3).

190   This insight into small-peptide signaling in Arabidopsis may help with identification of similar

191   mechanisms in crop plants for root-to-shoot mobilization of stress signals.

192

193   *A view to the future*

194   Genetic traits that sustain crop plant growth under moderate drought may come from multiple

195   sources, including natural genetic variation in wild relatives or bioengineering. Traditional

196   breeding has been the main strategy for exploiting the genetic diversity of adaptive traits in natural

197   alleles. The advent of genomic technologies and gene mapping tools such as GWAS and precision

198   genome editing with the CRISPR/Cas9 system became instrumental for the generation of new

199   alleles that can improve plant yield and performance under various stresses Molecular studies

200   using tissue/cell-specific promoters coupled with live microscopy techniques for real-time

201   visualization of cellular processes pave the way for analysis of drought responses network that can

202   be used as targets for various biotechnological approaches (Fig. 4) . Small molecules, such as

203   peptides or hormone agonists, may be useful for fine-tuning drought-response pathways while

204   preserving yield in agriculture (. Together, uncovering the physiology of plant responses to drought

205   in model system and translating that to crops will deliver new strategies to combat water scarcity.

206   Agriculture is a thirsty enterprise. Discovering ways to ameliorate agriculture's thirst will ease

207   competition for freshwater resources from increasing population growth.

FIGURE LEGENDS

Figure 1: The power of biotechnology to solve the problem of drought-induced food insecurity.

a) Most scenarios predict that the scarcity of water will increase in years to come. With the world´s population continuously raising, crop production must be duplicated to fulfill civilization´s basic needs. For this purpose, the efficiency of water usage in plants will need to be improved. b) Estimated world population for the 1990-2050-time period. Arrow indicates estimated number of people potentially living in water-scarce areas of the planet. c) Global arable land for agriculture for the 1990-2050-time period. Arrow indicate predicted demand of arable land to assure food security, given current rates of crop production per hectare. d) Global fresh water demand for agriculture for the 1990-2050-time period. Arrow indicates predicted decline in fresh water availability for agriculture in the current tendency of climate change and precipitations.

Figure 2: Root and shoot traits that account for drought resistance.

a-b) Plants first sense drought through their roots, where particular cell types such as stem cells, cells in the cortex and vasculature mediate adaptive responses towards water limitations. Roots can modulate their system architecture to c) maximize access to superficial humidity or delve into deep humid soil layers, and d) bend towards more humid soil zones (hydrotropism). e-f) In aboveground plant organs such as leaves and stem stomata work actively against dehydration. In water limiting conditions, stomata remain closed to reduce water loss.

Figure 3: Hormone signaling events underpinning drought.

231 Schematic representation of hormone signaling modules controlling drought adaptation. Plants

232 work against dehydration in all their organs such as leaves, vasculature and roots ABA, through

233 SnRK2, activates a variety of genes that cause stomata closure and improve water balance. When

234 drought is sensed in the roots, CLE25 peptide moves through the vasculature to leaves where

235 locally controls ABA biosynthesis and stomata closure. Brassinosteroids also play roles in

236 regulating plant drought response. Brassinosteroid pathway converge with ABA by activating

237 SnRK2 through downstream pathway component, BIN2 and *vice versa*. Independently of ABA,

238 brassinosteroid receptors (BRI1, BRL1, BRL3) modulate hydrotropic responses in the roots.

239 Vascular BRL3 receptor coordinates plant growth and survival under drought stress by promoting

240 the accumulation of osmoprotectant metabolites in the root tissues. Furthermore, non-canonical

241 auxin responses via EXO70A3 and PIN4 can modulate root architecture patterning and depth, to

242 improve water absorption from the soil improving drought tolerance.

243

244 **Figure 4: The promise of overcoming drought in agriculture.**

245 Various strategies can provide solutions to counteract drought and can be used to develop drought-

246 smart crops. Natural allelic variations found in plants can be selected to improve drought resistance

247 and yield. Traditional plant breeding approaches have successfully employed such useful traits to

248 obtain more resistant crop varieties in fields. Advancements in gene mapping tools such as GWAS

249 can explore the genetic diversity of drought resistance traits in natural alleles with nucleotide-level

250 precision. Genetic engineering of drought response markers at spatio-temporal scale and precise

251 genome editing with tools such as the CRISPR/Cas9 have opened new horizons to develop crops

252 with improved drought resistance without impairing yield. New techniques such as optogenetics

253 allow fine manipulation of cell/tissue specific responses to signaling and therefore increase growth

254 and plant resistance to drought. Bio-stimulants such as small peptides, hormone mimics and

255 receptor agonists can be used to designing better agrochemicals and fine-tune drought resistance

256 while preserving yield.

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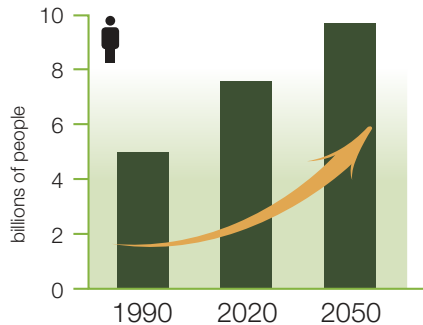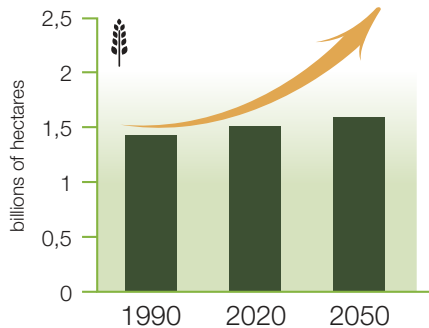413
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428   A.G. and A.I.C.-D wrote the manuscript. A.G. and A.R.-M. designed the figures. All authors

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432   The authors declare no competing or financial interests.

a

Year 2020 → Duplicate Crop Production → Year 2050

b

billions of people

10
8
6
4
2

1990   2020   2050

c

billions of hectares

2,5
2
1,5
1
0,5
0

1990   2020   2050

d

billions of cubic meters

5
4
3
2
1
0

1990   2020   2050

a

50 um

b

50 um

c

d

1 cm

high osmotic media

e

100 um

f

20 um

ABA

PYR/PYL
RCAR

Stomata
closure

SnRK2 → ABA-responding
genes

CLE25

BIN2

BRASSINOSTEROIDS

BIN2 ⊣ BRL3

Hydrotropism,
osmoprotectant
metabolites
accumulation

BES1 ← WRKYs/
TINY

RD26

CLE25

AUXIN

EXO70A3

IAA

Root system
architecture

PIN4

CLE25

Drought
sensing