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David and Goliath: what can the tiny weed *Arabidopsis* teach us to improve biomass production in crops?

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In the next decades, the world market for plant-derived products is expected to expand exponentially. Not only do we rely on plants to feed the growing world population, but plants will also play a pivotal role in providing a significant part of our increasing energy demands. Whereas in the 1960s the green revolution contributed to increase plant productivity, it is expected that biotechnological advances will further boost biomass production and plant yield. To do this effectively, it will be necessary to understand how the molecular machinery that determines yield parameters operates. Although of no direct economic significance, the model plant *Arabidopsis* can be used to find genes and regulatory networks controlling biomass production, which, in turn, can be applied for further growth improvement in other species including cereals.

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Introduction

The demand for more plant-derived products is increasing spectacularly because of the continuously growing human population, the increased consumption of animal products requiring more plant-derived feed and the need for bio-energy to provide an alternative to fossil energy. Whereas in the 1960s the green revolution immensely contributed to intensify plant productivity, biotechnological innovations are expected to drive a further increment of the ability of plants to capture light energy and convert it into useful products for humanity [1]. One important area for biotechnological improvement is the boosting of intrinsic yield and biomass production with a minimum input of water, fertilizers, and agrochemicals. Because yield is the most important trait for breeding, a considerable amount of (eco)physiological research has been conducted on crop yield performance [2,3]. In contrast, surprisingly little is known about the molecular networks underpinning plant yield [4]. Although not directly economically important, the model plant *Arabidopsis thaliana* offers a number of experimental advantages over crop species [5] and is, therefore, by far the best characterized in terms of its growth-regulating molecular mechanisms. Here, we review the current understanding of the molecular processes that govern biomass production in *Arabidopsis* and subsequently we evaluate to what extent this know-how can be implemented to enhance crop yields.

Yield-enhancing genes in *Arabidopsis*

Despite the complex nature of yield, many genes have been described in *Arabidopsis* that, when mutated or ectopically expressed, cause formation of larger structures, such as leaves or roots and, hence, more biomass. We will refer to such genes as 'Intrinsic Yield Genes' (IYGs). IYGs are involved in various processes whose inter-relationship is mostly unknown. In most cases, we do not even know how these genes cause enhanced growth and if the larger organs merely have more cells and/or whether cells are larger.

We compiled all *Arabidopsis* genes that have been reported to induce larger leaves, when ectopically expressed or mutated (Table 1). Genes that strongly delay flowering were excluded, although they generally have more and larger leaves. The IYGs belong to distinct functional classes, underlining the complexity of growth control and the great potential for further improvement by combining these different pathways (Figure 1). In the following sections, we will discuss functional classes of IYGs and their effect on leaf size.

Transcriptional regulation

It is not surprising that several transcription factors enhance growth when ectopically (over)expressed. Well-studied examples are GROWTH-REGULATING-FACTOR 5 (GRF5) and the interacting protein ANGUSTIFOLIA 3 (AN3/GIF1) [6]. For both *AN3* and *GRF5* overexpression, the increased leaf size results from increased cell numbers as the mature cell size is normal. The overexpression of two other members of the *GRF* transcription factor family, *GRF1* and *GRF2*, also produces larger cotyledons and leaves in *Arabidopsis* [7]. However, in this case, the enlarged leaf size is not the result of the production of more cells, but of the promotion of cell expansion.

Table 1

***Arabidopsis* genes leading to the formation of larger leaves when ectopically overexpressed (OE) or mutated (LOF).**

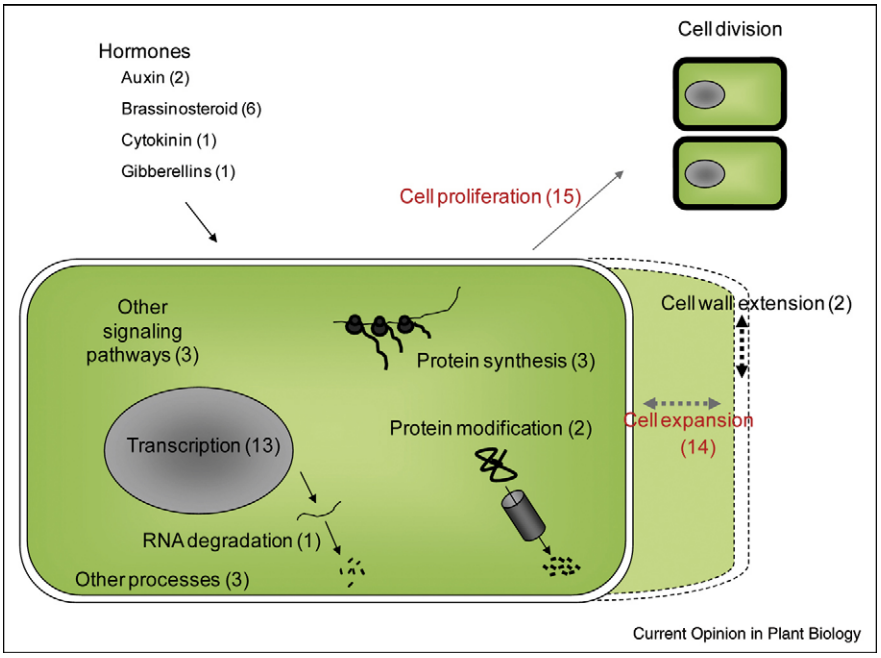
Gene	Encoded protein	Expression alteration	Refs
Transcriptional regulation			
ANT	Transcription factor AP-2	OE	[10]
ARF2	Transcription factor	LOF	[13]
ATAF2	NAC-domain transcription factor	OE	[9]
ATHB16	HDZip transcription factor	LOF	[53]
GIF1/AN3	Homolog of human SYT transcription activator	OE	[6]
GRF1	Putative transcription factor	OE	[7]
GRF2	Putative transcription factor	OE	[7]
GRF5	Putative transcription factor	OE	[6]
HRC1	At-hook transcription factor	OE	[47]
JAW	miRNA 319 (target: TCP2, 3, 4, 10, 24)	OE	[19,20••]
NAC1	NAM/CUC transcription activator	OE	[8]
OBP2	DNA-binding-with-one-finger (DOF) transcription factor	LOF	[54]
PPD	Putative DNA-binding proteins	LOF	[18•]
RON2	WD-40 transcriptional repressor	LOF	[15]
Protein synthesis and modification			
DA1	Ubiquitin receptor	LOF	[25••]
DHS	Deoxyhypusine synthase	LOF	[23,24]
EBP1	Homolog to human nucleolar ribosome biogenesis factor	OE	[22•]
TOR	Ser/Thr kinase	OE	[21•]
UBP15	Ubiquitin-specific protease	OE	[55]
Hormonal regulation			
Brassinosteroid			
ARGOS-LIKE	Unknown protein	OE	[31]
BEN1	Homologous to dihydroflavonol 4-reductase and anthocyanidin reductase	LOF	[28]
BRI1	Brassinosteroid receptor kinase	OE	[27]
DWF4	Steroid 22a hydroxylase	OE	[26]
EXORDIUM	Unknown protein	OE	[30]
TTL	Transthyretin-like	LOF	[29]
Auxin			
ARGOS	Unknown protein	OE	[12]
AVP1	H^+-pyrophosphatase	OE	[32]
Gibberellin			
GA20 oxidase	GA 20 oxidase	OE	[35,36]
Cytokinin			
HOG1	Cytokinin-binding protein	LOF	[38]
Other signaling pathways			
CLE26	CLV3/ESR secreted peptide ligand	OE	[43]
KLU	Cytochrome P450 monooxygenase	OE	[39•]
SRF4	Receptor-like kinase	OE	[42]
Cell wall extension			
EXP10	Expansin	OE	[17]
EXP3	Expansin	OE	[46]
Other			
ABAP1	Armadillo-BTB *Arabidopsis* Protein 1	LOF	[44••]
GRA	Unknown	Unknown	[56]
KAT2	3-Ketoacyl-CoA thiolase-2	LOF	[57]

Genes are classified according to function.

Another class of transcription factors, the plant-specific NAC protein family, also increases biomass production. Plants with high expression levels of *NAC1* produce larger leaves and also develop more lateral roots than wild-type plants [8]. Overexpression of another NAC-domain transcription factor, ATAF2, leads not only to increased biomass, but also, as a negative consequence, to leaf yellowing [9]. In the latter case, the larger leaves contained larger cells.

AINTEGUMENTA (ANT), a transcription factor of the AP-2 class, enhances organ size by maintaining meristem competence and, therefore, increasing cell numbers [10]. Plants overexpressing *ANT* also have larger flowers that

Figure 1



Different processes in which Intrinsic Yield Genes (IYGs) are involved. For some of these genes, the process involved in the growth phenotype, cell proliferation, or cell expansion, is known (in red). Numbers of IYGs belonging to each class are given in parentheses.

are attributed to more cells in the sepals and larger cells in petals, stamen, and carpels [11]. *ANT* is induced by ARGOS, a protein with a still unknown function in auxin signaling, but that, when ectopically overexpressed, leads to production of larger organs with more cells [12].

Inversely, several transcription factors appear to repress plant growth, as reducing their expression level enhances yield. Mutants of the AUXIN RESPONSE FACTOR 2 (ARF2), thought to function as a transcriptional repressor, form larger organs with more and larger cells than those of wild-type plants [13]. A specific mutant allele of *ARF2*, *megaintegumenta*, dramatically increases seed size and seed weight [14]. In this mutant, the expression of *ANT* is prolonged.

The *ROTUNDA2* (*RON2*/*LEUNIG*) gene encodes a WD40 protein that putatively acts as a transcriptional co-repressor. The *Arabidopsis rotunda2* (*ron2*) mutant produces longer petioles and wider leaf blades with larger cells [15]. ROTUNDA2/LEUNIG interacts with histone deacetylase and the MEDIATOR components to repress transcription [16]. Interestingly, a transcriptome analysis of the *lug* mutant showed that the *EXP10* gene, by itself causing production of larger leaves when overexpressed [17], is part of the multiple genes regulated by RON2 [16].

Deletion of the *PEAPOD* (*PPD*) locus, which contains two adjacent homologous genes (*PPD1* and *PPD2*) that encode plant-specific putative DNA-binding proteins, results in the formation of larger, more dome-shaped leaves [18•]. The excess growth in the center of the blade is explained by an extended proliferation period of dispersed meristematic cells, such as precursors of stomata stem cells and vascular cells.

Downregulation of the TEOSINTE BRANCHED1/CYCLOIDEA/PCF (TCP) transcription factors TCP2, TCP3, TPC4, TCP10, and TCP24, through overexpression of the microRNA, miR-JAW (miR319), triggers the formation of larger, more serrated leaves [19]. Interestingly, single mutants of *TCP2*, *TCP4*, or *TCP10* only have slightly enlarged leaves when compared to *jaw-D* mutants, showing partially redundant functions of the different TCP factors [20••].

Protein synthesis and modification

Besides transcriptional control, regulation of translation has a profound effect on plant growth. The TOR kinase promotes growth by regulating numerous biological processes, including translation of ribosomal components. Ectopic expression of the *Arabidopsis TOR* enhances both root and shoot growth, essentially as a consequence of enlarged cell sizes [21•]. *TOR* overexpression enhances expression of EBP1, an ortholog of the human epidermal growth factor receptor-binding protein, ErbB-3. In humans, EBP1 is part of ribonucleoprotein complexes binding to rRNA precursors and small nucleolar RNA species in the nucleoli. EBP1 activity regulates the

production and assembly of the translational machinery. Ectopic expression of the *EBP1* gene from potato (*Solanum tuberosum*) in *Arabidopsis* produces enlarged rosette leaves, a phenotype similar to that provoked by *TOR* overexpression [21•,22•]. The *EBP1* overexpression phenotype is partly the result of increased cell numbers early in leaf development when the cell division rate is high. In addition, EBP1 also affects cell size at later stages of leaf development: when division is arrested, cell size is increased [22•]. Expression of *TOR* and *EBP1* is closely correlated across various developmental stages [21•], suggesting that EBP1 could be a target of TOR and act downstream of TOR kinase on the mRNA translation machinery.

Deoxyhypusine synthase (DHS) is involved in protein synthesis by activating the eukaryotic initiation factor 5A (eIF-5A) that regulates the translocation of newly formed mRNAs from the nucleus to the cytoplasm. Transgenic plants with downregulated DHS activity have delayed leaf senescence, high root biomass, and an increased rosette size [23]. Constitutive suppression of *DHS* expression also has some negative effects, such as delayed bolting, a phenotype that is not observed when *DHS* expression is silenced by a leaf-specific promoter [24].

Ubiquitination of proteins plays an important role in proteolysis and signaling. A mutation in the *DA1* gene, encoding a ubiquitin receptor, leads to the production of a dominant negative protein affecting DA1 as well as other DA1-related (DAR) proteins. Plants harboring the *da1-1* mutation have rounder and larger leaves, and produce larger and more seeds [25••]. The number of cells in these larger organs is increased because of longer cell proliferation time. Interestingly, a mutation in the E3 ligase BIG BROTHER/ENHANCER OF DA1 (BB/EOD1) in the *da1* mutant synergistically enhances the seed and organ size phenotype of *da1-1*, suggesting that these two genes act in parallel pathways to control organ size [25••].

Hormonal regulation

One main function of plant hormones is to regulate growth processes. Therefore, it is not surprising that several genes that alter the hormonal status contribute to enhanced plant growth and biomass production. In particular, brassinosteroids, auxins, gibberellins, and cytokinins seem to play pivotal roles in promoting plant growth.

Enhanced expression of the brassinosteroid receptor, BRI1, stimulates growth of leaf petioles, similarly to plants ectopically expressing the brassinosteroid biosynthetic enzyme DWARF4 (DWF4) [26,27]. The *Arabidopsis BEN1-1D* (BRI1-5 Enhanced 1-1 Dominant) gene, encoding a protein homologous to dihydroflavonol 4-reductase, regulates the levels of brassinosteroids. A mutation in *BEN1* leads to production of elongated leaves [28]. When the TRANSTHYRETIN-LIKE protein (TTL), a potential BRI1 downstream target, is mutated, plants also produce larger leaves and longer petioles [29]. *EXORDIUM* (*EXO*) is upregulated by brassinosteroids and has been shown to regulate the expression of different brassinosteroid-responsive genes [30]. The overexpression of *EXO* under the control of the CaMV 35S promoter results in the production of larger leaves with longer petioles as well as in the promotion of root growth. Finally, overexpression of another brassinosteroid-induced gene *ARGOS-LIKE* (*ARL*), with some sequence homology to *ARGOS*, also enhances plant growth by increasing cell expansion [31].

Interfering with auxin fluxes appears to affect plant growth as illustrated by the H^+-pyrophosphatase-encoding gene, *AVP1*. AVP1 has been suggested to control auxin transport and its overexpression dramatically enhanced growth of both shoots and roots [32]. The larger leaves in *AVP1*-overexpressing plants contain more cells. Interestingly, AVP1-overproducing plants are also more tolerant to dehydration stress [33].

Gibberellins have been known for a long time for their effect on cell elongation [34]. Gibberellin 20-oxidase catalyzes pivotal steps in the synthesis of gibberellins and, as expected, transgenic lines ectopically expressing *GA20-oxidase1* are 25% taller at maturity and have larger leaves [35,36].

Cytokinins typically inhibit root growth and stimulate shoot development [37]. Recently, by means of an antisense construct, downregulation of HOG1, a cytokinin-binding protein, has been shown to increase leaf size and seed yield [38].

It remains possible that, besides the hormones discussed above, other plant growth regulators play a role in controlling plant development and architecture. Overexpression of the cytochrome P450 mono-oxygenase, KLU, leads to the formation of larger leaves and flowers that might be a consequence of enhanced production of an unknown growth-promoting signal [39•]. The recent finding of strigolactones as regulators of lateral branching [40,41] illustrates the scope for potential discovery of new growth-promoting substances.

Other signaling pathways

Overexpression or downregulation of specific genes encoding signal-transducing molecules has been shown to increase plant growth, often without a good understanding of the molecular mechanism. For example, STRUBBELIG-RECEPTOR FAMILY4 (SRF4) is part of the receptor-like kinase (RLK) class that allows signal transfer across membranes. Plants overexpressing *SFR4*

develop larger leaves, but the cellular process is still unknown [42]. There is also evidence that CLAVATA3/ESR (CLE) peptides are involved in regulating plant growth. Overexpression of *CLE26* increases rosette area and root length [43].

Cell division

Although several IYGs enhance growth by affecting cell proliferation, we found no reports in which direct interference with the basic cell cycle machinery led to enhanced shoot growth. Although not a part of the cell cycle machinery, Armadillo-BTB *Arabidopsis* Protein 1 (ABAP1) has recently been shown to control the cell proliferation rate by limiting mitotic DNA replication [44••]. Plants with reduced *ABAP1* expression produce larger leaves containing more cells. ABAP1, therefore, seems to limit DNA replication by interacting directly with pre-Replication Complex (pre-RC) components and/or by repressing *pre-RC* genes through its interaction with the transcription factor TCP24.

Cell expansion

Increased cell size directly affects growth and requires structural modification and extension of the cell wall. Expansins (EXPs) constitute a family of cell-wall loosening proteins involved in cell wall extension without hydrolytic breakdown of the major structural components [45]. Ectopic expression of *EXP10* under its own promoter leads to the formation of larger leaves and longer petioles. This increase in leaf size is the consequence of larger cells [17]. Similarly, the plants overexpressing *EXP3* produce larger leaves, but the responsible mechanism is unknown [46].

In summary, growth can be stimulated by modifying (hormonal) signaling and protein abundance through effects on transcription, translation, and proteolysis (Figure 1). These pathways converge, by largely unknown mechanisms, on cell division and cell expansion to affect the overall organ growth. By assembling these observations, we were able to draft a first outline of a growth-regulatory network (Figure 2).

Relevance of *Arabidopsis* yield genes for crop improvement

Several genes that promote growth in *Arabidopsis* also stimulate growth in other species, including monocots. For example, in tobacco (*Nicotiana tabacum*), overexpression of the *Arabidopsis* brassinosteroid biosynthetic gene, *DWF4*, and of the transcription factor *ANT* enhances growth [26] and increases organ size [10], respectively. The *Arabidopsis AVP1* also promotes root growth and drought tolerance in tomato (*Solanum lycopersicum*) [33]. Also in tomato, overexpression of *HRC1* leads to increased organ size [47]. In potato (*Solanum tuberosum*), high levels of the potato *EBP1* expression cause larger plants with larger cells [22•].

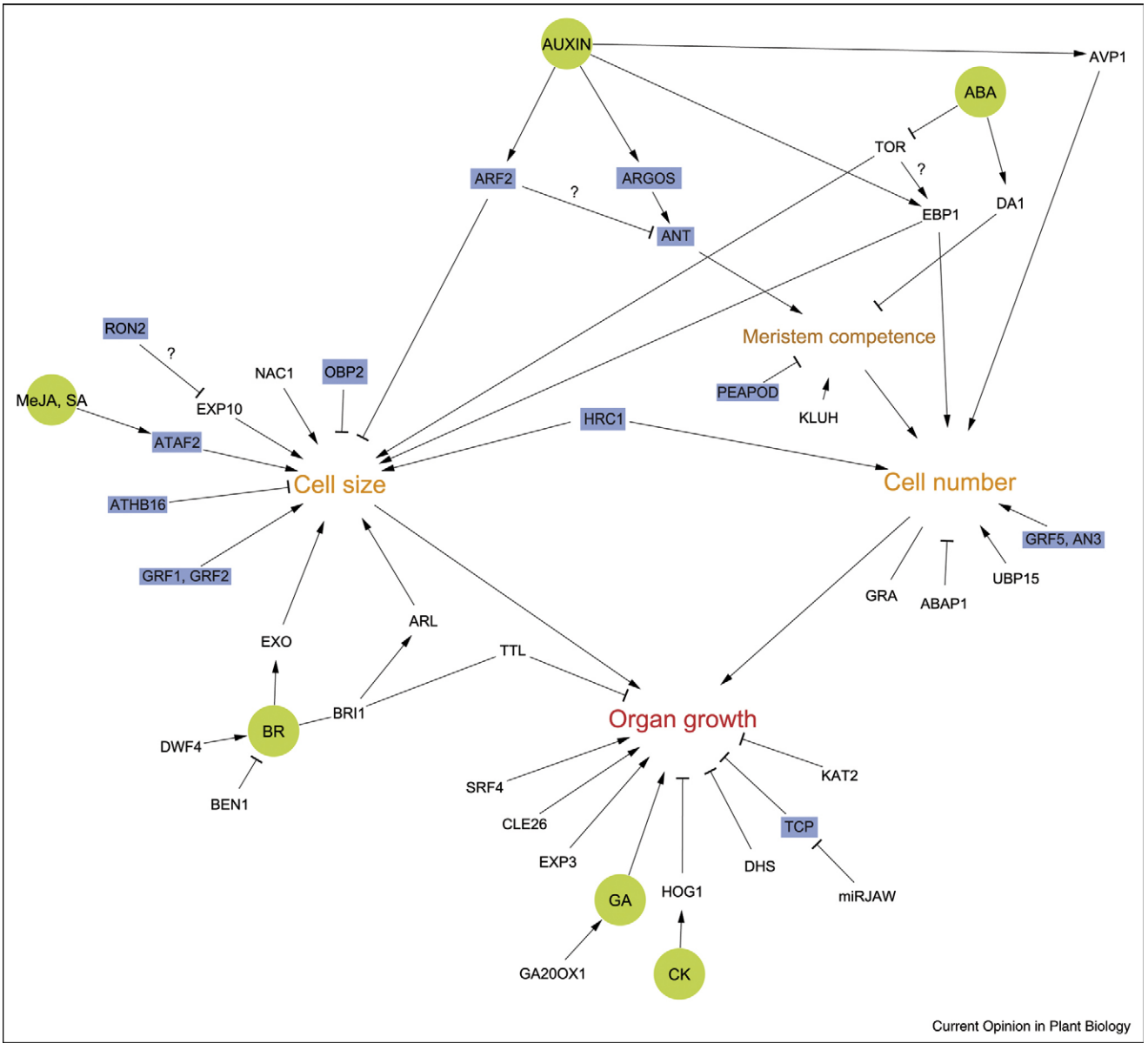
Transgenic rice (*Oryza sativa*) plants ectopically expressing the rice GA20-oxidase are twice as large as control plants [48]. In transgenic rice plants with inducible *EXP4* expression, EXP4 protein levels and seedling growth are closely correlated [49].

In other cases, positive effects in *Arabidopsis* plants were not reproduced in other plants. For example, constitutive downregulation of DHS increased the biomass production in *Arabidopsis*, but had no or pleiotropically negative effects on growth and development in tomato [50]. Nevertheless, by and large, the experimental evidence demonstrates that in many cases, genes selected for their positive effect on growth in *Arabidopsis* exert a similar effect in other species, including monocotyledonous crops. Thus, the data suggest that the small model plant *Arabidopsis* can deliver insights and genes that can be used to increase productivity in crops.

The need of a systems biological approach for understanding yield

A major drawback in interpreting the effects of IYGs on plant growth and biomass production is that measurements are made in different laboratories worldwide, with different growth conditions and *Arabidopsis* ecotypes, making comparisons on the basis of literature data treacherous. Future research on the effects of IYGs on plant growth could benefit from growth measurement data of plants grown under standardized conditions, with the same ecotype and appropriate controls, such as non-transgenic seed stocks harvested from plants grown simultaneously with transgenic lines under uniform conditions. The latter is highly relevant because growth of seedlings from seed batches of different origin and age can vary dramatically, creating a potential source of artifacts. Transgenic lines with enhanced growth characteristics need to be thoroughly characterized using standardized analytical procedures to quantify the cellular basis of the phenotype. Currently, only in some cases are data available on the cellular nature of growth enhancement. As such, modified expression of *ABAP1*, *AN3*, *ANT*, *ARGOS*, *AVP1*, *DA1*, *GRA*, *GRF5*, *JAW*, *KLUH*, *PPD*, and *UBP15* appears to result from enhanced cell division, although it is not clear whether the rates or duration are increased. Other genes, such as *ARL*, *ATAF2*, *ATHB16*, *GRF1*, *GRF2*, *EXO*, *EXP10*, *NAC1*, *OBP2*, *RON2*, and *TOR*, apparently provoke formation of larger cells; again, it is unclear if this is due to rate or duration of expansion. Only in very few cases (*ARF2*, *EBP1*, and *HRC1*) both cell division and expansion are affected. Although for most transgenic lines with enhanced growth characteristics, the molecular function of the perturbed gene is broadly known, the downstream molecular mechanisms that cause altered growth phenotypes are not. For example, of the 37 lines described here, only six transcriptome analyses have been published (for *ARF2*, *ATAF2*, *JAW*, *KLU*, *RON*, and *TOR*) [9,14,16,19,21•,39•]. Moreover, these micro-array data correspond to different

Figure 2



Control of organ growth by Intrinsic Yield Genes (IYGs) in *Arabidopsis*. Blue rectangles and green circles show transcription factors and plant hormones, respectively. ABA, abscisic acid; CK, cytokinin; GA, gibberellin; BR, brassinosteroid; SA, salicylic acid; MeJA, methyl jasmonate.

plant tissues, developmental stages, and growth conditions and are, therefore, not easily comparable.

The lines with increased biomass production are an excellent basis to progress from observations on individual genes to a systems-level understanding of the yield-regulating network. To achieve this goal, the transcriptome of all *Arabidopsis* lines with increased biomass production needs to be analyzed. Bioinformatics analysis of these expression data will allow the generation of candidate genetic networks linked to physiological processes that either positively or negatively correlate with enhanced growth. Purification of protein complexes [51] using as bait proteins whose modulation affects yield, will help to place IYGs in such regulatory networks and select which genes can be combined to maximize plant growth. Besides transcriptomics, metabolomics will further help decipher the molecular basis of enhanced growth. A large-scale metabolic profiling of *Arabidopsis* recombinant inbred lines with contrasting biomass production has already revealed a close link between biomass and a specific combination of metabolites [52•]. To unravel the relevance of putative growth-regulating networks, key components of such networks will need to be further

functionally analyzed by knock-down and overexpression approaches. Genetic variation between *Arabidopsis* accessions offers the possibility to study whether specific alleles of IYGs correlate with growth properties. Genetically, it will be important to cross various transgenic lines with enhanced growth properties to determine whether the observed effects are additive or synergistic. The network and expertise obtained with such a systems approach in the model species *Arabidopsis* will ultimately allow us to design efficient strategies to engineer crop species with superior yield capacity.

Conclusions

A relatively large number of genes have been found that can increase growth and biomass in *Arabidopsis*, of which several can also increase yield in crop species. However, at the same time, we have limited insight into the growth parameters or molecular changes that occur in these plants. To engineer crops with superior biomass production, systems-level studies are urgently needed to bring together the still fragmented data in a single developmental framework.

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