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植物器官大小相关基因研究进展

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摘要: 器官大小是植物形态的一个重要特征,而且具有严格的种属特异性。植物器官大小虽然受到外在的环境因素(如光照、营养等)的影响,但它是由内在特有的细胞数目和细胞大小决定的。许多基因能通过转录调节、蛋白合成、激素调节或松弛细胞壁等途径作用于植物细胞繁殖和 / 或细胞扩张,它们的过表达或缺失表达能改变植物器官大小和加快植物生长。尽管如此,这些基因是通过相对独立的途径起作用,在植物中难以阐明一个相对整合的器官大小基因调控网络,这也是亟待解决的问题。目前,一些与器官大小相关的基因已经应用于农作物育种,并培育出显著增大的农作物品种,这也证实了利用器官大小基因进行植物品种选育的可行性。因此,通过研究药用植物器官大小的基因,在分子水平上有目的地调控器官的大小和形态,是缓解当前许多药用植物面临的资源紧缺、枯竭、濒危困境的可考虑途径之一。

关键词: 植物器官大小; 基因; 细胞增殖; 细胞扩张
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Research Progresses on Genes Involved in Regulation of Plant Organ Size

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Abstract: Organ size is an important morphological trail in plants, and shows significant differences among species. Organ growth is influenced by environmental factors, such as light and nutrients; however, it is determined by the intrinsic information of cell number and cell size. A large number of genes involved in regulation of cell proliferation and/or cell expansion have been identified, and their up-regulated or down-regulated expression change organ size and accelerate organ growth by means of transcription regulation, protein synthesis and modification, hormonal regulation and cell-wall loosening, and so on. In spite of this, these genes act through relative independent pathways, making it difficult to demonstrate an integrated regulation network in plants. Further challenges will be the regulation pattern and molecular changes in different plant species. Several genes participated in organ growth have been used in crop breeding, and produced significantly large crops. Similarly, characterization of the genes involved in organ size control of Chinese herbs to artificially promote organ size and morphology at the molecular level will contribute to overcome the shortage and endangerment of medicinal plants.
Key words: Plant organ size; Gene; Cell expansion; Cell proliferation

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Plants show various organ size from species to species, even those closed related. Organ size possesses rigorous species specificity in plant from germination to mature, and is precisely controlled by intrinsic mechanism of plant growth and development. Leaf size occupies an important position in diverse plant organ, especially affects the energy capture and other physiological activities of plants[1–2]. Due to the comprehensiveness and complexity determined by internal and external factors, the regulation mechanism that sets the final organ size is one of difficult aspects in plants.

Although the final size of organs is influenced by environmental factors, such as light and nutrients, the developing organs were regulated by intrinsic information about their final size. For example, organ size shows amazing consistency among the individuals with the same species, while significant differences may exist among the species belonging to the same genus. Both cell number and cell size are related to setting of growth and development of plant species-specific organ size, which are consequences of coordination between cell proliferation and cell expansion[3–6]. After cells leave the meristem, cell division cycle activates and cells begin to expand. Along with the water entering vacuole, the crosslink among the polymers located at cell wall begins loosening, which coupled with endoreduplication. These processes promote cell size and increase cell number, and the change from cell proliferation to cell expansion or division determines cell number and results in the final organ size[4,7]. A number of research on regulating plant organ size were carried out to trace the genes or related regulators participated in the processes of cell proliferation and/or cell expansion, and try to characterize their functions (Table 1). Their gain or loss of function phenotypes revealed promotive effects on final organ size. However, many identified regulators were revealed working in relatively independent pathways making it difficult to develop an integrated regulation model of plant organ size.

Here, we reviewed the reported genes involved in organ size of plant in these years and divided them into four main categories based on their functions. Moreover, a perspective on the feasibility of utilizing these genes in special plants, such as medicinal herbs was provided.

Table 1 Genes involved in plant organ size

Gene	Encoded protein	Expression alteration	Possible mechanism	Reference
Transcription related				
ANT	Transcription factor AP-2	OE	Increase cell number	[8 – 11]
ARF2	Transcription factor	LOF	Mediate gene expression in response to auxin and promote cell division and expansion	[12 – 13]
ATAF2	NAC-domain transcription factor	OE	Enlarge cell significantly	[14]
AtHB16	HDZip transcription factor	LOF	Promote cell expansion	[15]
BIGPEATALp	MADS-box transcription factor	LOF	Increase cell size and interfere with postmitotic cell expansion	[16]
CIN	TCP transcription factor	LOF	Promote cell division or cell proliferation	[17]
GIF/AN3	Homolog of human SYT transcription activator	OE	Promote cell proliferation and increase cell number	[18]
GRF1	Putative transcription factor	OE	Increase cell size and regulate cell expansion	[19]
GRF2	Putative transcription factor	OE	Increase cell size and regulate cell expansion	[19]
GRF5	Putative transcription factor	OE	Increase cell number and maintain cell size	[18]
HRC1	At-hook transcription factor	OE	Increase both cell size and cell number	[20]
JAGGED	Putative transcription factor	OE	Promote cell proliferation	[21 – 25]
JAW	miRNA-319 (Target: TCP2,3,4,10,24)	OE	Reduce expression level of TCP transcription factors and promote cell proliferation	[26 – 27]

Continued

Gene	Encoded protein	Expression alteration	Possible mechanism	Reference
NGATHA	B3 transcription factor	LOF	Regulate both cell number and size via control over cell cycling	[28]
OBP2	DOF transcription factor	LOF	Increase both cell number and cell size	[29]
PPD	Putative DNA-binding proteins	LOF	Prolong the period of dispersed meristematic cell proliferation	[30]
RON2	WD-40 transcription repressor	LOF	Promote cell expansion and cell division	[31]
Protein synthesis and modification				
BIG BROTHER	E3 ubiquitin ligase	LOF	Increase cell number	[32]
DA1	Ubiquitin receptor	LOF	Increase cell number	[33 – 34]
EBP1	ErbB3 binding protein	OE	Promote cell proliferation or cell expansion in different periods	[35 – 38]
MED	Mediator complex subunit	LOF	Promote both cell proliferation and cell expansion	[39 – 40]
TOR	Ser/Thr kinase	OE	Increase cell size; an enhancer of *EBP1*	[41]
UBP15	Ubiquitin-specific protease	OE	Control cell proliferation and increase cell number	[42]
Hormonal regulation				
Auxin				
ABP1	Auxin binding protein	OE	Promote cell expansion or cell proliferation based on auxin concentration	[42 – 47]
ARGOS	Unknown protein	OE	Enlarge cell size and increase cell number	[48 – 51]
AVP1	H^+-pyrophosphatase	OE	Increase cell division	[52 – 53]
Bassinosteroid				
BEN1	Homologous to dihydroflavonol 4-reductase and anthocyanidin reductase	LOF	Regulate brassinosteroid levels and promote cell division	[54]
BRI1	Brassinosteroid receptor kinase	OE	Promote cell elongation and differentiation	[55]
EXO	EXOPDIUM protein	OE	Increase transcript levels of the BR-up-regulated genes involved in the mediation of BR-promoted growth and active cell division	[56]
Gibberellin				
GA20 oxidase	GA20 oxidase	OE	Promote cell elongation	[57 – 59]
Cytokinin				
HOG1	Cytokinin-binding protein	LOF	Affect the expression of cytokinin primary response genes to promote cell division	[60]
Cell-wall loosening agent				
EXP3	Expansin	OE	Promote cell expansion and increase cell elongation	[61]
EXP4	Expansin	OE	Increase cell size and mediate cell-wall loosening	[62]
EXP10	Expansin	OE	Increase cell length significantly and cell number inconspicuously	[63]
Others				
ABAP1	Armadillo-BTB Arabidopsis Protein 1	LOF	Increases cell division rates	[64]
AGG3	G protein γ subunit	OE	Increasing the period of cell proliferation	[65]
CNR	Putative *fw* 2.2 ortholog	LOF	Increase cell number	[66]
fw2.2	Similar to the human oncogene c-H-ras p21	LOF	Control carpel cell number	[67]
KLU	Cytochrome P450 monooxygenase	OE	Increase cell number and promote organ growth in a non-cell autonomous manner	[68 – 69]
RPT2a	Paralog molecule of the RPT2 subunit	LOF	Promote cell expansion and increase DNA replication	[70]

OE: Overexpression; LOF: Loss of function.

1 Transcriptional regulation

It is no wonder that transcription factor participate in organ growth and enhance organ size when ectopically expressed. Intensive researches have been launched to study how transcription factors AINTEGUMENTA (*ANT*) and JAGGED (*JAG*) work. *ANT* is required for flora organ development by regulating cell division of integument and controls cell division and organ size during the development of buds. Loss of *ANT* function reduces the size of lateral organ by decreased cell number. Conversely, ectopic expression of 35S:*ANT* enhances *ANT* function and enlarges embryos and buds attributed to increased cell number, but the extrinsic shape of these organ is not altered. In the fully differentiated organs, the cells overexpressed *ANT* display neoplasia activity, and then give birth to callus and form roots and buds occasionally. Therefore, *ANT* regulates cell proliferation and organ growth through maintaining meristematic capability of cells during the organogenesis[8–11]. The recent studies also revealed that *ANT* and related genes, AINTEGUMENTA-LIKE6 (*AIL6*) and AINTEGUMENTA-LIKE7 (*AIL7*), functionally act together in the meristem of young floral primordial, carpel margin and shoot apical through auxin transport[71–73].

JAGGED, encoding a putative transcription factor with a single C_2H_2 zinc-finger domain, expresses in all tissues and organs, and is a growth promoter characterized by stronger tissue-expression specificity. Loss of *JAG* function incompletely restricts the development of lateral organ[21–23]. The correlation between expressional threshold of *JAG* in the petal and the redundant cell activities in cell cycle indicates that *JAG* governs the growth by maintaining or activating the activity of cell cycle. In addition, the phenotypes of loss of *JAG* function are identical with those overexpressed cyclin-dependent kinase inhibitor, and the activities of cell cycle are suppressed, which is another evidence revealing the function of *JAG* on growth controlling[24–25]. Unlike other growth factors (e.g. *BIG BROTHER* and *ANT*), *JAG* also promotes morphogenesis of several lateral organs[8,22–23].

The growth-regulating-factor family members (*GRF1*, *GRF2*, and *GRF5*) and their interacting protein AN3/GIF1 have been confirmed as positive regulators for organ size in *Arabidopsis*. Overexpression of all these genes lead to increase of leaf size, however, the result is caused by two processes. *GRF1* and *GRF2* enlarge leaf size contributed to cell expansion, while *GRF5*/*GIF1* increase the size by producing more cells[18–19].

Gain-of-function of several transcription factors show repressive effects on cell proliferation or cell expansion, their expression levels were artificially downregulated to promote organ size and yield. Mutant of AUXIN RESPONSE FACTOR2 (*ARF2*) significantly enhanced final seed size and weight by promoting both cell proliferation and cell expansion[12]. Meaningfully, the expression level of *ANT* in this mutant increased[13], speculating that these two genes were possibly complementary to regulate cell processes.

Down-regulation members of TEOSINTE BRANCHED1 / CYCLOIDEA / PROLIFERATION CELL FACTOR1 (*TCP*) transcription factor family remarkably enhanced leaf size and number through overexpression of *miRNA-319*[26], and up-regulation of *miRNA-319* separately lead to similar results[27], however, single mutants of *TCP* only exhibited slightly enlarged leaves[26], indicating that microRNA probably restricted the expression of *TCP* and participated in regulation of organ size directly or indirectly.

Silent *PPD* increased leaf size by prolonging the period of dispersed meristematic cell division[30]. Down-reguation expression of *NGATHA* also enlarged leaves, flowers and cotyledons as well as stimulating root growth[28].

2 Protein synthesis and modification

Except for transcription factor, protein regulation at translation level plays a profound role in organ growth. EBP1, a member of the PA2G4 family, was identified as an epidermal growth factor receptor (ErbB3)-binding protein. Expression of *EBP1* is

ubiquitous in all tissues and cells[35–36] and rigidly regulated in plants. The level is the highest in developing organs, which closely related to genes involed in ribosome biogenesis and function. During early peroid of organogenesis, *EBP1* promotes cell proliferaton, influences cell-size threshold for division, and limits the period of meristematic activities. In postmitotic cells, it advances cell expansion. *EBP1* is indispensable for expression of cell cycle genes; *CyclinD3*;*1*, ribonucleotide reductase 2 and the cyclin-dependent kinase *B1*;*1*. The regulation of these genes by *EBP1* is dose and auxin dependent, and upregulated *EBP1* levels decreases the endogenous RBR1 protein, results in the release of the E2F-dependent transcription of these cell cycle genes and then, promotes cell proliferation, which may be the mechanism that EBP1 set the final organ size[37]. EBP1 accelerates growth, enlarges leaves and enhances cold tolerance by enhancing ribosome biogenesis and the concomitant translation of cold induced transcription factors and downstream protective protein under cold stress in transgenic *Arabidopsis* plants[38].

Target of rapamycin (*TOR*) encodes Ser/Thr kinase and promotes organ growth by regulating plenty of biological processes, such as translation of ribosomal components. Overexpression of *TOR* also promotes *EBP1* level, which is validated in various development stages[41]. The interrelation between *EBP1* and *TOR* suggests that EBP1 could be a target of TOR and act downstream of TOR kinase on the mRNA translation machinery.

Ubiquitination of proteins occupies a key part in plant growth and exhibits promotive effect in mutation. Encoding a putative ubiquitin receptor, *Arabidopsis DA1* (*AtDA1*, DA means “large” in Chinese), as well as seven closely similar genes *DA1-related* (*AtDAR*) controls final seed and organ size by limiting the duration of cell proliferation in early stage of organogenesis. *da1-1*, a mutant changing a conserved amino acid at position 358 of *AtDA1*, has a negative influence towards *AtDA1* and *AtDAR* on transgenic *Arabidopsis* and functionally independent of *ANT*, *AXR1* and *ARF2*. Overexpression of *da1-1* significantly enlarges seed, flower, leaf, and seedling size of wild-type *Arabidopsis*[33]. Interestingly, *EOD1* (means enhancer of *DA1*) significantly enhances the seed and organ size phenotype of *da1-1*, and is identified as mutant of another plant growth repressor *BIG BROTHER*[34], indicating that *BIG BROTHER* and *DA1* act in parallel pathways to control organ size.

Mediator complex subunit plays a key role in shade avoidance and stress responses. Some members of mediator complex subunit functionally reduce the final organ size in plant. Overexpression of *MED25* limits organ size with smaller and fewer cells, while loss of *MED25* function enlarges organ size with large and inconspicuously increased number of cells, implying that *MED25* controls organ growth by reducing both cell proliferation and cell expansion. The mutants of *MED25*, called *eod8-1* and *MED25-2*, also enlarge floral organs and significantly enhance the *da1-1* phenotypes in Arabidopsis. *MED25* functions associating with DA1 to control final organ size by restricted cell proliferation independent of *MED25*-mediated phytochrome signaling and jasmonate[39]. *MED8*, another member of mediator complex subunit, shows similar effect with *MED25* by restricting cell proliferation. However, *MED8* is functionally independent of *MED25*; they possibly transmit distinct signals from different classes of activators to the RNA polymerase II complex to initiate transcripts of their respective downstream target genes involved in organ size control[40].

3 Hormonal regulation

It is well known that hormones play a dominant role in signaling transformation network, and together with other signals, regulates cell processes, such as cell division, elongation and differentiation in plant cells. In particular, the roles of auxin, brassinosteroid, gibberellins, and cytokinins in organ size have been studied in plants.

3.1 Auxin

ABP1 (Auxin binding protein 1) shows higher expression in young meristem, such as terminal buds, root tips and spires, than in other tissues and organs[43]. Overexpression of *ABP1* enlarges mesophyll cell, while antisense suppression of *ABP1* dramatically reduced cell expansion and inconspicuously influences on cell division induced by auxin[44]. *ABP1* is functionally related to the concentration of auxin, it promotes cell elongation with low level of auxin, while increases cell division with high level of auxin[45]. Due to promoting cell elongation with the TIR1 pathway and cell division with RBR pathway in root and regulating expression of the genes involved in auxin response, ABP1 was considered as a key regulator for root growth and auxin response in cell cycle[46–47].

A regulator of plant organ size highly induced by auxin, auxin-regulated gene involved in organ size (*ARGOS*), was identified from *Arabidopsis*. Expression of sense or antisense *ARGOS* cDNA enlarges or reduces aboveground organs in transgenic plants, ascribing to alterations in cell number and the duration of organ growth. Ectopic expression of *ARGOS* prolongs both the neoplastic activity of leaf cells and the expression of *ANT* and *CycD3*;*1*. Further studies had showed that loss of function of *ANT* interrupts the organ enlargement in the plants overexpressing *ARGOS*, indicated that *ARGOS* functions upstream of *ANT* to impact on meristematic ability of organ cells. The induction of *ARGOS* by auxin is weaken or totally suppressed in auxin-resistant1 (*axr1*) and overexpression of *ARGOS* partially regains *axr1* organ size. These discoveries suggested that *ARGOS* conducts auxin signals downstream of *axr1*, regulates cell proliferation and organ growth through *ANT*[48]. Expression of rice *ARGOS* gene in *Arabidopsis* enlarged organ size by promoting both cell division and cell expansion, however, the transgenic rice (*Oryza sativa*) overexpressing *OsARGOS* did not reveal any organ size change compared to the control, implying that the mechanism of *OsARGOS* on controlling organ size in rice is probably different from in *Arabidopsis*[49]. Ectopic expression of a Chinese cabbage (*Brassica rapa*) *BrARGOS* in *Arabidopsis* increase the size of all tissues and organs, solely by enhanced cell proliferation, but no contribution from cell expansion[50]. Expression of *ARGOS* gene driven by DMW promoters accelerates growth, significantly increases leaf size and enlarges flowers in transgenic tobacco (*Nicotiana tabacum*), and these phenotypic traits are steadily shown in T2 transgenic plants, but function of *ARGOS* in cell proliferation in tobacco is far weaker than in *Arabidopsis*[51].

AVP, a gene encoding H^+-pyrophosphate, has been served as a controller of auxin transport. Upregulate expression of *AVP* enlarged shoot and root size by promoting cell proliferation[52–53].

3.2 Brassinosteroid

In generally, brassinosteroid (BR) enhances shoots and roots growth by stimulating cell division. *EXO* is a BR-up-regulated gene and enhances the transcription of genes participated in the mediation of BR-promoted growth. Overexpression of *EXO* results in petiole elongation, leaf expansion and root growth[56]. Another brassinosteroid regulator *BEN1* also elongates the *Arabidopsis* organs when mutated[54]. Besides, *BRI* encodes a brassinosteroid-sensitive receptor kinase and enlarges leaf petioles[55].

3.3 Gibberellins

Gibberellin (GA) plant hormones are indispensable for cell expansion, stem elongation and flower development. Gibberelin 20-oxidase (GA20ox) is the key enzyme in the GA biosynthesis pathway and catalyzes the oxidation and elimination of carbon-20 to synthesize bioactive C-19 GAs[57–58]. Overexpression of *GA 20-oxidase* increases the level of endogenous GAs and the transgenic Arabidopsis exhibited elongated hypocotyls, enlarged leaves and 25% taller than wild-type seedling[59]. In five *GA20ox* genes from *Arabidopsis* named *AtGA20ox1*, *AtGA20ox5*, *GA20ox1*, -2, and -3 were the dominant paralogs in the regulation of organ growth, they significantly promoted floral organ growth and other development. *AtGA20ox1* contributed more

in internode and filament elongation, *AtGA20ox2* mainly acted in flowering time and silique length. However, *AtGA20ox3* was functionally independent of *AtGA20ox1* and *AtGA20ox2* at most developmental stages, including the floral transition[74–75].

3.4 Cytokinins

Cytokinins are a kind of plant hormones that promote branching and leaf, shoot development. *HOG1*, an encoded gene of cytokinin binding protein, shows negative effect in plant stature by overexpression. In the antisense suppression lines, *Arabidopsis* plants with increased leaf size, profuse branching and more seed production were obtained, because of the function of *HOG1* on promoting cell division[60].

4 Cell-loosen agents

Expansins are proteins involved in cell wall extension and cell enlargement, and it maintains the major structure of a cell when regulating the process. As expected, ectopic expression of genes coding expansins (*EXP3*, *EXP4*, *EXP10*, et al) under control of 35S-CaMV promoter gives rise to the formation of larger leaves in *Arabidopsis*[61–63].

The achievements highlighted here provide new insight in controlling plant organ growth, with however, little understanding on the regulation pattern and molecular changes in different plant species. Therefore, more studies should be carried out to understand the connection across various pathways regulating organ size and illustrate an integrated regulation network in plants. In addition, how artificially added factors (fertilizers, phytohormones, humidity, et al) influence these growth pathways is also a challenge in this field.

The discoveries on genes related to organ size also motivate people to promote organ size of plants by engineering the genes. Deepen and comprehensive investigation on genes involved in organ size promote the crops and herbs to meet the market demand, and exhibits important implications in enhancing the quality and quantity of crops and plants. By far, genes involved in organ sizes have been applied in crop plants, maize (*Zea mays*) and tomato (*Lycopersicum esculentum*) with large size had been cultivated by regulating these genes[66–67], but no similar researches were found in medicinal plants. As special group of plants, herbal medicine always plays key role in human health, and the yield is important matter of concern. In reality, many herbal medicines encounter resource shortage and the resource obtained via existing methods is incapable to meet clinic and market demands. Characterization of the genes involved in organ size control from Chinese herbs in order to artificially regulate organ size and morphology at the molecular level will contribute to overcome the shortage and endangerment of medicinal plants. With the development of Herb Genome Program including whole genome sequencing of medicinal plants with endangerment or/and those of great medical and pharmaceutical importance[76], cloning and characterization of genes involved in organ size of medicinal plants become realistic. Plant genetic engineering, a series of technique originated in molecular biology and used widely in present researches, is well able to fulfill the steps in the studies. In addition, lots of successful examples in model plants and crops can be taken as guidance for similar studies in medicinal plants. Enlarging the size of leaves or whole plants is one of considerable and feasible ways to raise yield, especially on the condition that the active ingredients of quite a few herbal medicine remains unclear. Undoubtedly, attentions should be drawn to some critical questions in the area. Such as, whether there is any change of total chemical components and pharmacological effects occur in transgenic medicinal plants, how transformation of alien genes influences the synthesis pathways of secondary metabolites in medicinal plants, etc. Further and extensive studies should be carried out to enhance final organ size with the genes and to understand how they influence growth and development of medicinal plants.

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