A REVIEW: MOLECULAR REGULATION OF STOMATAL DEVELOPMENT RELATED TO ENVIRONMENTAL FACTORS AND HORMONES IN PLANTS

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Abstract. Plants regulate leaf transpiration rate and water potential by changing the number of stomata and their rate of opening and closing. Stomata act as turgor-operated valves for gas exchange and water evaporation based on environmental needs. During stomatal development, various transcription factors and related genes are involved in the reception or transduction of environmental factors and hormones. Recent studies have led to significant advances in our understanding of intercellular signaling, the underlying pathways, and the polarity of the asymmetric division that controls stomatal development. The endogenous and exogenous factors that regulate these elements have also been identified. However, the mechanism of stomatal formation and development is highly complex and several morphogenesis-related questions are still unresolved. In this review, the molecular basis of stomatal development, including transcription factors, functional genes, and regulatory pathways, is described in detail. The connection between stomatal development and environmental factors such as CO_2, light, temperature and air humidity is discussed. In addition, the influences of plant hormones on stomatal development are sketched out in the review. We also highlight critical questions requiring future research and form a detailed list involving in gene functions and trait changes in mutants.
Keywords: *stomata, molecular mechanism, epidermal patterning factors, bHLH transcription factors, leucine-rich repeat receptor-like proteins*

Introduction

Stomata are apertures typically observed on plant outer leaf layers; they maintain the optimal balance between CO_2 uptake and water loss as a way to adapt environmental conditions in plants (Ni, 2012). In primary leaves of Arabidopsis, stomatal formation involves three types of cells: meristemoid mother cells (MMCs), guard mother cells (GMCs), and meristemoids (Behzadi et al., 2014). A protodermal cell develops into a stoma via three rounds of unequal cell divisions. First, the epidermal cell differentiates into a MMC through a series of unknown steps. The MMC then undergoes an asymmetric division to produce a small meristemoid cell and a stomatal-lineage ground cell (SLGC). The GMC develops into two GCs that flank a central pore to constitute a stoma (Bergmann and Sack, 2007). In addition, a SLGC can form satellite meristemoids (SMs) by spacing asymmetric division, with the SMs gradually differentiating into stomata. Most stomata are formed from SMs in this fashion. In addition to their balancing function, stomata play a significant role in water, carbon, and nutrient cycles.

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Thorough investigation of stomatal regulation is therefore essential for understanding plant physiological responses to the environment and their physical functions (Von et al., 2002).

The traditional model explains stomatal development and distribution in terms of cell developmental lineages, cell–cell interactions, and long-distance signaling. In monocotyledons, stomata are arranged in chains parallel to leaf veins (Geisler et al., 2000). In Arabidopsis and other dicotyledons, however, stomatal distribution on the leaf surface is irregular and individual stomata are spaced from one another (Serna and Fenoll, 2000). Although in-depth examinations would be beneficial to understand gas exchange and to reduce moisture loss, such investigations can be very difficult because of this stomatal variation and the complex relationship between stomatal development and the environment.

Many studies have recently shown that stomatal development is a tightly controlled process. The various transcription factors, secreted protein, protease and some regulatory pathways have been shown to play an important role. While several environmental and hormonal factors are known to affect stomatal development, very little is known about the molecular mechanism for these changes. In this review, we describe stomatal distribution patterns and formation, signaling pathways, and genes related to stomatal development accordingly, and discuss directions for future research. We also form a detailed list involved in genes function and trait changes in mutants (*Table 1*).

Table 1. *Genes with mutations known to affect stomatal development in plant*

Locus	Symbol	Mutant phenotype (or overexpression phenotype)	Identity	References
EPIDERMAL PATTERNING FACTOR 1	EPF1	Increase stomatal densities	Cysteine-rich secreted peptide	Hara et al., 2009
EPIDERMAL PATTERNING FACTOR 2	EPF2	Increase the number of MMCs	Cysteine-rich secreted peptide	Hara et al., 2009
STOMAGEN	STOMAGEN	Reduce stomatal density	Cysteine-rich secreted peptide	Sugano et al., 2010
CHAL-LAH/EPFL6	CHAL	Increase stomatal density	Cysteine-rich secreted peptide	Abrash and Bergmann, 2010
Too Many Mouths	TMM	Stomatal clusters in leaves and no stomata in stems	Leucine-rich repeat receptor	Geisler et al., 2000
STOMATAL DENSITY AND DISTRIBUTION	SDD1	Higher stomatal density and some clusters	Subtilisin processing protease	Von et al., 2002
SPEECHLESS	SPCH	Fails to form stomata	bHLH transcription factor	MacAlister et al., 2007
MUTE	MUTE	Fails to form stomata	bHLH transcription factor	Pillitteri et al., 2007
FAMA	FAMA	Fail to progress into GCs and instead continue dividing	bHLH transcription factor	Ohashi-Ito and Bergmann, 2006
SCREAM/ICE1	SCRM	Fails to form stomata	bHLH transcription factor	Kanaoka et al., 2008
SCREAM2	SCRM2	Fails to form stomata	bHLH transcription factor	Kanaoka et al., 2008
PHYTOCHROME-INTERACTING FACTOR 4	PIF4	Fail to produce more stomata	bHLH transcription factor	Casson et al., 2009
FOUR LIPs	FLP	Induce the formation of clusters of four or more GCs	R2R3 MYB transcription factors	Lee et al., 2014
CO2 RESPONSE SECRETED PROTEASE	CRSP	More stomata at the elevated CO2 concentration	Extracellular protease	Engineer et al., 2014
High carbon dioxide	HIC	Increase stomatal density	3-keto acyl coenzyme A synthase	Gray et al., 2000
Carbonic anhydrase 1, 4	CA1, CA4	Increase stomatal density	Carbonic anhydrase	Hu et al., 2010; Engineer et al., 2014

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Locus	Symbol	Mutant phenotype (or overexpression phenotype)	Identity	References
RETINOBLASTOMA-RELATED	RBR	Promoting initial GC identity, but unable to maintain commitment	Similar to a human protein called Retinoblastoma	Matos et al., 2014
CONSTITUTIVE PHOTOMORPHOGENIC 1	COP1	Producing stomatal clusters	Ubiquitin Ligase	Liu et al., 2008
CONSTITUTIVE PHOTOMORPHOGENIC 10	COP10	Producing stomatal clusters	Ubiquitin Ligase	Delgado et al., 2012
Phytochrome B	phyB	Fail to produce more stomata	Red light photoreceptor	Casson et al., 2009
YODA MAPK(kk)	YDA	Fails to form stomata	Mitogen activated protein kinase	Lampard et al., 2009
BRI SUPPRESSOR1	BSU1	Massive stomata formation	Phosphatase	Kim et al., 2012
Cytochrome	CYP707A1	Prevent stomatal closure at high RH (Overexpression phenotype)	ABA catabolism protein	Arve et al., 2015; Jalakas et al., 2018
BRI1-ASSOCIATED RECEPTOR KINASE 1	BAK1	ABA insensitivity in stomatal closure	BRASSINOSTEROID-INSENSITIVE 1 ASSOCIATED RECEPTOR KINASE	Shang et al., 2016
ANGUSTIFOLIA3	AN3	Decreased stomatal index (loss-of-function) clusters of stomata (overexpression phenotype)	Homolog of the human transcription co-activator	Meng et al., 2018
CONVERGENCE OF BL AND CO2 1/2	CBC1/2	Stomata in leaves closed tighter	Mitogen-activated protein kinase kinase kinase	Hiyama et al., 2017
BLUE LIGHT-DEPENDENT H+-ATPASE PHOSPHORYLATION	BHP	Impairments of stomatal opening and H+-ATPase phosphorylation in response to blue light	Raf-like protein kinase	Hayashi et al., 2017
ABA-INSENSITIVE PROTEIN KINASE1	AIK1	Stomatal closing is less sensitive to ABA; slightly greater stomatal density and significantly increased stomatal index	MAPKKK20	Li et al., 2017
MPK12	MPK12	Stomatal CO_2-insensitivity phenotypes of a mutant *cis* (CO_2-insensitive) and the higher degree of stomatal opening	MAP kinase	Jakobson et al., 2016
SLOW ANION CHANNEL-ASSOCIATED 1	SLAC1	Dramatically impair stomatal closure induced by CO_2	S-type anion channel protein	Vahisalu et al., 2008
H^+-ATPase translocation control 1	PATROL1	Impair stomatal opening in response to low CO_2 concentration and light	Protein with a MUN domain	Hashimoto-Sugimoto et al., 2013; Engineer et al., 2016
HIGH LEAF TEMPERATURE 1	HT1	Constitutively open stomata and impaired stomatal CO_2 responses	Protein kinase	Jakobson et al., 2016
Open Stomata 1	OST1	Insensitivity to ABA promotion of stomatal closure and ABA inhibition of stomatal opening	Protein kinase	Mustilli et al., 2002
ABA INSENSITIVE 1/2	ABI1 and ABI2	ABA-induced stomatal closing is abolished	Protein phosphatase 2C	Hirayama et al., 2007
BIG/CIS1	BIG/CIS1	Fail to show reductions in stomatal density and index, but display inhibition of stomatal opening with eCO_2 concentration	Calossin-like protein	He et al., 2018
BLUE LIGHT-DEPENDENT H+-ATPASE PHOSPHORYLATION	BHP	Impairments of stomatal opening	Raf-like kinase subfamily in the MAPKKK family	Hayashi et al., 2017
Phot1 and phot2	Phot1 and phot2	Blue light-dependent stomatal opening and the H^+-ATPase activation were absent	Light-activated receptor kinases	Doi et al., 2004

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Rac-interactive binding motif-containing protein 7	RIC7	Promoted light-induced stomatal opening	Rac-interactive binding motif-containing protein	Hong et al., 2016
ENHANCED RESPONSE TO ABA 1	ERA1	More closed stomata phenotype; stomatal opening induced by blue light was impaired	Farnesyl transferase beta subunit	Jalakas et al., 2017
Photosystem II Subunit S	PsbS	Less stomatal opening in response to light (over-expression)	Integral membrane protein	Głowacka et al., 2018
RESPIRATORY BURST OXIDASE 1	RBOH1	Impaired eCO_2-induced stomatal closure and the compromised eCO_2-enhanced water use efficiency as well as the heat tolerance	RESPIRATORY BURST OXIDASE	Zhang et al., 2018
JASMONATE ZIM DOMAIN 2	JAZ 2	Impaired pathogen-induced stomatal closing	JASMONATE ZIM DOMAIN (JAZ) proteins	Gimenez-Ibanez et al., 2017
MORE AXILLARY GROWTH 2	MAX2	More widely opening stomata or increased stomatal conductance	MORE AXILLARY GROWTH protein	Piisilä et al., 2015

Basic signal transduction and molecular regulation

Various transcription factors and other proteins involved in stomatal development have been studied along with their related genes. The encoded proteins include a family of epidermal patterning factors (EPFs), subtilisin-type proteinases (stomatal distribution and density 1 [SDD1]), leucine-rich repeat receptor-like proteins (TOO MANY MOUTHS [TMM]), basic helix-loop-helix (bHLH) transcription factors, and MAPK phosphatases (Geisler et al., 2000; Von et al., 2002; Hara et al., 2009; Jakobson et al., 2016). These studies, to some extent, have expounded the mechanisms of stomatal formation and development.

Role of EPF

EPF genes encode a protein family of cysteine-rich peptides that include 11 member ligands in Arabidopsis. The EPF family peptides are classified into four subgroups based on their amino acid sequences. Some proteins have been identified as involved in stomatal development, such as epidermal patterning factor 1 (EPF1), epidermal patterning factor 2 (EPF2), STOMAGEN/EPFL9, and CHAL etc. (Hara et al., 2009; Abrash and Bergmann, 2010; Sugano et al., 2010).

EPF1 and EPF2

EPF1 and EPF2 affect the formation of stomatal precursors through distinct yet overlapping functions. Asymmetric cell division and the formation of stomatal clusters or pairs is controlled by EPF1, which is produced in meristemoids, GMCs, and GCs. Mature leaves lacking *EPF1* consequently show an increase in the number of stomata and frequent stomatal pairing. EPF2 inhibits meristemoid formation and promotes the formation of pavement cells. The *epf2* mutant increases stomatal densities and leads to the formation of small, arrested stomatal lineage cells. In contrast, ectopic expression of *EPF2* suppresses entry divisions, which leads to an epidermis composed only of pavement cells. The double mutant *epf1*/*epf2* displays additive effects, causing greatly increased stomatal densities, stomatal pairing, and arrested cells (Hara et al., 2009; Hunt

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and Gray, 2009). Over-expression of either *EPF1* or *EPF2* has been found to suppress stomatal formation, but has revealed that they act on different developmental processes. EPF1 enforces the one-cell spacing rule, whereas EPF2 inhibits the population of cells from acquiring the stomatal lineage fate. *EPF2* can partly substitute for *EPF1* in function, but *EPF2* cannot be replaced by *EPF1*. In addition, *EPF2* expression requires the bHLH transcription factor SPEECHLESS (*SPCH*) and a MAPK (YODA [*YDA*]), suggesting that EPF2 is mediated by the MAPK cascade (Hara et al., 2009). EPF1 and its primary receptor ERECTA-LIKE1 (ERL1) target MUTE as a bHLH protein that controls the transition from meristemoids to GMCs and specifies the proliferation-to-differentiation switch within the stomatal cell lineages, while MUTE directly induces ERL1 (Du et al., 2018).

Although the function of *EPF1* and *EPF2* has been studied deeply in many aspects. Compared with EPF1, however, the function of EPF2 still remains some unknown domains that need to study further in the future. For example, how do the EPF2 peptide and ERECTA receptor affect the downstream signaling components? What proteases activate EPF2?

STOMAGEN/EPFL9

STOMAGEN/EPFL9 is an EPF known to positively influence stomatal development (Von et al., 2002). Over-expression of *EPFL9* shows increased stomatal density and clustering, while loss of *EPFL9* function leads to reduced stomatal density with no clustering. *EPFL9* acts independently of *EPF* to regulate stomatal density and control stomatal clustering, while acts independently of *SDD* to control both stomatal density and clustering (Hunt et al., 2010). In another study, it was showed that STOMAGEN controls stomatal development by binding with the TMM receptor protein to compete with EPF1 and EPF2. Genetic analysis has revealed that TMM is epistatic to STOMAGEN, which suggests that stomatal development is mediated by competitive binding of positive and negative regulators to the same receptor. Loss of *STOMAGEN* function results in fewer stomata. Conversely, *STOMAGEN* over-expression increases stomatal cluster formation and stomatal density (Hunt and Gray, 2009).

Even though the placement of stomata relative to one another has been demonstrated to be controlled by intercellular signaling via several EPFs, the extracellular proteases that function in EPFs pathways still remain unknown (Lee et al., 2015). Environmental signals that regulate the stomatal development via the extracellular propeptides EPFs or the protease SDD1 have still not been certified. Fortunately, the mechanism underlying the interaction of β-carbonic anhydrase and CO_2 RESPONSE SECRETED PROTEASE (CRSP) that influences the action of EPF2 in the CO_2 signaling pathway for stomatal development has been recently uncovered (Engineer et al., 2014). The elucidation of the detailed functions of EPFs other than EPF2 and their impacts on extracellular proteases and environmental signaling during stomatal development obviously requires further investigation.

CHAL

Similar to EPF1 and EPF2, CHAL inhibits stomatal formation. *CHAL* was studied during a screening designed to detect suppressors of *tmm* mutant, and only presented a phenotype in the presence of the *tmm* mutation. Although excess stomata were observed on leaf surfaces of *tmm* mutants, stomata were completely absent from stems.

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Interestingly, stomata reappeared on stems when *CHAL* was knocked out in the *tmm* mutant. Over-expression of *CHAL* requires ERECTA family (ERf) to suppress stomatal development. These differing results indicate that TMM may play a buffering role in the ERf receptor system, preventing EPF1 and EPF2 from disturbing the formation of normal epidermal patterns by absorbing excess CHAL (Abrash and Bergmann, 2010).

Role of TMM

TMM, a LRR-RLP receptor protein, negatively regulates stomatal density and placement. STOMAGEN positively regulates stomatal development, while EPF1 and EPF2 negatively regulate stomatal development by interacting with TMM as ligands. Loss of *TMM* function fails to orient and suppress asymmetric divisions of cells adjacent stomata or their precursors; in addition, loss-of-function mutants undergo a reduced number of divisions, resulting in the premature conversion of meristemoids into GMCs (Geisler et al., 2000). TMM plays an important role in cell-cell communication and perceives information regarding transient contiguous cell confirmation and location (Bergmann and Sack, 2007). The secretory peptides encoded by EPFs are expressed in meristemoids, with their activity dependent on the function of TMM and ERf members. ERfs and TMM work cooperatively to inhibit stomatal production. EPFs require TMM or ERfs to certify their over-expression phenotypes, which indicates the importance of these three proteins in EPf perception (Horst et al., 2015; de Marcos et al., 2016).

Role of SDD

SDD1 is a negative regulator of stomatal development, which encodes a subtilisin-like serine protease. SDD1 affects both protoderm and neighboring cell fates. During the development of neighboring cells, the shift from pavement cells to SM precursors may be controlled by a SDD1-dependent reaction signal in meristemoids/GMCs. Whether the meristemoid/GMC response causes the neighboring cell shift or instead triggers or extends *SDD1* expression is unclear (Von et al., 2002). Loss of SDD1 function leads to properly spaced but denser stomata. In one investigation, a 1.5-fold increase in stomatal density and index were reported in two *sdd1-1* mutants of Arabidopsis (Bergmann and Sack, 2007). *SDD1* overexpression causes a two- to four-fold decrease in stomatal density but does not considerably alter leaf and epidermal cell sizes (Von et al., 2002).

Role of bHLH transcription factors

In plants, bHLH transcription factors constitute an evolutionarily ancient group known to specify cellular identity. Some homologous bHLH proteins play important roles in the determination of the fate of successive stomatal precursor cells. For example, SPCH, MUTE, and FAMA act to activate cellular transition about stomatal development, share 88% structural homology and 39% sequence homology. Despite their similarities, they can not functionally replace each other during stomatal development because of the specific features of each protein (Ohashi-Ito and Bergmann, 2006).

SPCH

The *SPCH* gene is the key factor in the process of protodermal cell division into MMCs. *SPCH* involves in a basic pathway that initiates asymmetric division in the stomatal lineage (MacAlister et al., 2007; Vatén et al., 2018). The *spch* mutant fails to

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produce interlocking pavement cells and promote stomatal lineages, while over-expression of *SPCH* raises the number of cells in the stomatal pathway. In addition, SPCH can prolong meristemoid identity, as loss of SPCH function leads to that meristemoids divide significantly fewer times. SPCH is also a target of brassinosteroid (Br) and MAPK signaling, and is an integration point for environmental information that allows for appropriate patterning and optimization of stomatal density under changing conditions (Ohashi-Ito and Bergmann, 2006).

MUTE

MUTE is a bHLH protein that controls the transition from meristemoids to GMCs, which promotes the differentiation of meristemoids into stomata (Pillitteri et al., 2007; Mahoney et al., 2016). The *mute* mutant fails to form stomata, but has no effect on meristemoid formation. Over-expression of *MUTE* has been shown to shift all epidermal cells toward stomata. The promoter of *MUTE* is not active in meristemoids, but is specifically activated in late-stage meristemoids. It was suggested that *MUTE* promoters binding with one finger regulatory elements is important for regulation (Mahoney et al., 2016). Because it is difficult to predicate the number of meristemoid divisions, how meristemoids regulate the timing of *MUTE* expression and the end of meristemoid division is unclear.

FAMA

FAMA, which controls GC fate, is expressed during the symmetric division that produces the two young GCs, but not in mature stomata (Ohashi-Ito and Bergmann, 2006). This protein likely acts as a transcriptional activator to regulate the transition from GMCs to GCs during symmetric division. Loss of FAMA function results in lack of mature stomata, while it develops clusters of GMCs or incipient GCs. Over-expression of *FAMA* converts non-stomatal cells to GCs in *fama* mutant plants (Ohashi-Ito and Bergmann, 2006). Matos et al. (2014) found that FAMA must bind to another protein, RETINOBLASTOMA-RELATED (RBR), to control the GMC to GC transition. These two proteins cause a permanent transition from stem cells to GCs. When the partnership between FAMA and RBR is broken, reversion of the GCs into stem cells can be observed.

SCRM and SCRM2

SCRM and SCRM2 are two additional bHLH proteins, which promote cellular transitions during stomatal development. Both of these proteins share high sequence homology and encode bHLH-type leucine zipper nucleoproteins. SCRM and SCRM2, which exist in cells of all stages, are similar in expression and function (Kanaoka et al., 2008). A *scrm* single mutant displays phenotypes similar to the *fama* mutant, while the *scrm-scrm2* double mutant produces occasional *spch*-like columns. It was showed that SCRM and SCRM2 interact with SPCH, MUTE, and FAMA. Map-based cloning has shown that SCRM is one of the key regulatory factors during cold stress, indicating that the ability of plants to adapt to environmental conditions may be related to developmental factors (Serna and Fenoll, 2000). Both environmental and developmental factors regulate stomatal development, which implicates SCRM as a participant in the integration of environmental signals directly into the stomatal differentiation pathway (Lee et al., 2017).

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Taken together, these three bHLH family members-SPCH, MUTE, and FAMA-control formation, amplification, division, and final differentiation in stomatal development (*Fig. 1*). Remarkably, the SPCH protein can be phosphorylated by MPK3 and MPK6, whereas no such phosphorylation has been reported for MUTE and FAMA. SPCH generates stem cells and triggers their asymmetric division, while MUTE controls the meristemoid-to-GMC transition. SPCH, MUTE, and FAMA form obligate heterodimers with ICE1/SCRM and SCRM2, but not among themselves. These genes non-redundantly and positively regulate the stomatal development. However, interaction with RBR is inadequate to define the feature of FAMA and indicate a version of FAMA that behaves like MUTE or SPCH (Davies and Bergmann, 2014). It is necessary to study the larger interacted complexes that contribute to stomatal lineage by further work on protein interactions. It is also needed to identify what kind motifs are involved in these protein interactions.

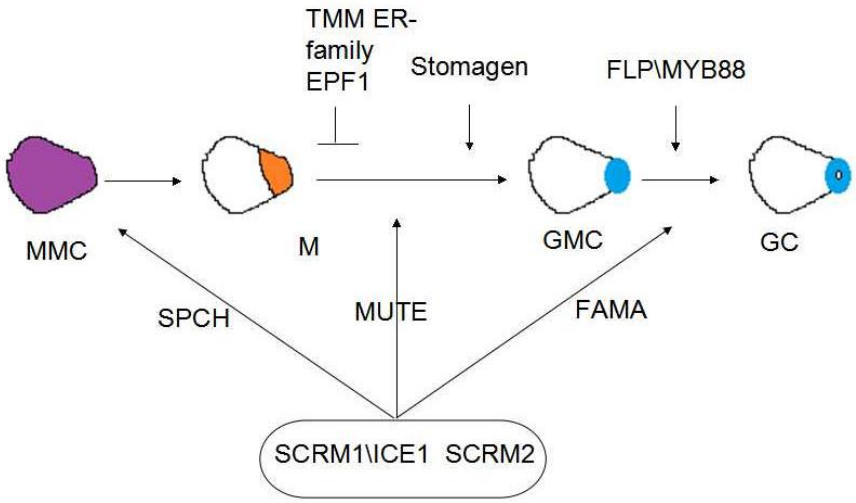

Figure 1. *Model of the differentiation steps regulated by sequential actions of bHLH transcription factors and related genes. MMC: meristeoid mother cell (purple), M: meristemoid (orange), GMC: guard mother cell (blue), GC: guard cell (blue with circle)*

Role of MAPK cascades

The MAPK signaling pathway controls cell fate and division during stomatal development. MAPK cascades are organized into a core module comprising three protein kinases: a MAPK, a MITOGEN-ACTIVATED PROTEIN (MAP) kinase kinase (MKK), and a MAP kinase kinase kinase (MAPKKK). YDA, a MAPKKK in the MAPK cascade, negatively regulates stomatal development. The associated signaling pathway consists of YDA, MKK4/5/7/9, and MPK3/6/9. The YDA-MKK4/5-MPK3/6 complex negatively regulates processes involved in the formation of GMCs from MMCs and of GCs from GMCs. YDA-MKK7/9, in contrast, positively controls these processes (Lampard et al., 2009). Loss of *AtYDA* function generates a clear increase in the production of leaf stomata in Arabidopsis, whereas expression of constitutively active mutants of *AtYDA* causes repressed stomatal formation in leaf epidermis. Furthermore, epidermal cells of *yda* mutant cotyledons display excessive entry divisions, thereby failing to prevent division of neighboring cells that connect two stomatal lineage cells. Asymmetry of cell fates is also compromised in *yda* mutants.

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Over-expression of *YDA* leads to a significant decrease in stomatal density and the rate of water loss (Bergmann and Sack, 2007). *ABA-INSENSITIVE PROTEIN KINASE1 (AIK1)* gene encodes MAPKKK20 and positively regulates ABA-induced stomatal closure. The stomatal closing in *aik1* mutants was less sensitive to ABA than that in wild-type plants. In addition, the *aik1* mutants exhibit slightly greater stomatal density and significantly increased stomatal index. It was revealed that MKK4 and MKK5 could interact with AIK1 in vivo (Li et al., 2017). As another MAPK cascade**,** MPK12 regulates the stomatal aperture. Loss of MPK12 function results in the stomatal CO_2-insensitivity phenotypes and the higher degree of stomatal opening. It was showed that MPK12 interact with the protein kinase HIGH LEAF TEMPERATURE 1 (HT1) to inhibit the activity of HT1. Because of the higher degree of stomatal opening, the instantaneous water use efficiency is lower in *mpk12* mutants, suggesting that MPK12 is a important regulator of stomatal conductance (Jakobson et al., 2016).

The influence of environmental factors

Role of CO_2 concentration

In the plant epidermis, the adjustable stomatal pores formed by GCs allow CO_2 to enter for photosynthesis and water from transpiration to escape to the atmosphere. Plants accommodate to a continuous rise in atmospheric CO_2 concentration by adjusting stomatal density and closing stomata (Hu et al., 2015; Engineer et al., 2016). Gray et al. (2000) have identified a gene, designated as *HIC* (for high carbon dioxide), that is related to the signal transduction pathway responsible for regulating stomatal numbers at elevated CO_2 (eCO_2). *HIC* encodes a protein similar to 3-ketoacyl coenzyme A synthase, which is expressed specifically in GCs. Loss of *HIC* function results in an increase in stomatal density for reacting to a doubling of CO_2. *HIC* is the first gene to be identified that affects plant developmental responses to global changes in atmospheric composition. β-carbonic anhydrase (βCA) is a CO_2-binding protein that functions early in the CO_2 signaling pathway for stomatal development. Two βCAs, CA1 and CA4, were identified that function in the CO_2 response. Double mutants (*ca1 ca4*) result in an inversion in response to eCO_2 by increasing stomatal development (Hu et al., 2010). Over-expression of *CA4* and *CA1* could refresh CO_2-induced stomatal responses in double mutants. The *ca4* mutant shows a slightly altered sensitivity to the CO_2 stimulus (Hu et al., 2015; Engineer et al., 2016).

A novel CO_2-induced extracellular protease, CRSP, has been identified as a mediator of CO_2 regulation of stomatal development during atmospheric CO_2 elevation. Interaction of CA1, CA4, and CRSP degrades the pro-peptide EPF2, repressing stomatal development. However, EPF2 is vital to CO_2 regulation of stomatal development (Engineer et al., 2014). Future research should focus on if feedback modulation results in CO_2 regulation of EPF2 and CRSP transcripts and what are the transcriptional regulators regulating the eCO_2 response. SLOW ANION CHANNEL-ASSOCIATED 1 (SLAC1) is an S-type anion channel protein, which plays a important role in stomatal closure in response to eCO_2. Loss of *AtSLAC1* function dramatically represses stomatal closure induced by CO_2 (Vahisalu et al., 2008; Hedrich and Geiger, 2017).

Stomatal opening is promoted by the activation of H^+-ATPases (AHA1) in the guard cell plasma membrane, and eCO_2 concentration inhibits proton efflux by plasma membrane AHA1 (Hashimoto-Sugimoto et al., 2013). The *PATROL1* gene encodes a

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protein with a MUN domain, which is involved in the membrane trafficking of neurotransmitter release. Loss of *PATROL1* function results in the impaired stomatal opening in response to low CO_2 concentration, disturbing the normal plasma membrane targeting of H^+-ATPases (Engineer et al., 2016).

HT1 is a protein kinase and an essential regulator of stomatal CO_2 responses. Loss of HT1 function results in constitutively stomata opening and repressed stomatal CO_2 responses (Jakobson et al., 2016). The open stomata 1 (OST1) protein kinase is involved in CO_2- and ABA-induced stomatal closing (details in ABA section). It was suggested that HT1 phosphorylates the OST1 protein kinase, which inactivates OST1 (Mustilli et al., 2002; Tian et al., 2015). BIG/CIS1 is a calossin-like protein, which regulates CO_2-induced stomatal closure (He et al., 2018). Loss of BIG/CIS1 function fails to show reductions in stomatal density and index, but displays inhibition of stomatal opening with eCO_2 concentration. It was showed that BIG/CIS1 is only demanded in eCO_2-induced stomatal closure, suggesting the signaling pathways of CO_2-mediated promotion of stomatal closure are distinguishable with inhibition of opening (He et al., 2018). Because BIG/CIS1 is associated with auxin transport, further research should focus on if disruptions to auxin signaling underlie the BIG/CIS1 stomatal mutant phenotype. These studies could help researchers to choose plant germplasm for adapting to CO_2 levels.

Role of light

Light intensity affects stomatal density and the stomatal index, which play an important role in cell fate decisions in the epidermis (Casson et al., 2009). CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1), a E3 ubiquitin-protein ligase, is a repressor of light-controlled stomatal development (Liu et al., 2008). A current study showed that COP1 degrades ICE through ubiquitination pathways in leaf abaxial epidermal cells. Loss of *COP1* function results in the ICE proteins accumulate in the nuclei of leaf abaxial epidermal cells. Interestingly, light impairs the COP1-mediated degradation of the ICE to induce stomatal development, which upregulates EPF2 activity at the transcriptional level, thereby conferring proper stomatal spacing and distribution. Thus, it is likely that the COP1-ICE-EPF2 signaling module integrates light signals into developmental programs that regulate stomatal development (Lee and Park, 2017). ANGUSTIFOLIA3 (AN3) is a positive regulator of stomatal development, which interacts with the *COP1* promoter to regulate light-induced stomatal development. Loss of *AN3* function results in decreased stomatal index, whereas overexpression of *AN3* leads to clusters of stomata (Meng et al., 2018). These suggest that the AN3–COP1–E3 pathway regulates stomatal development with the integration of light signaling. COP10 is another dominant component of stomatal-lineage divisions, which represses stomatal fate and adjusts the initiation frequency and extension of stomatal lineages. Loss of *COP10* function results in the production of stomatal clusters. COP10 regulates genetically in parallel with SDD1 and does not affect epidermal cell differentiation (Delgado et al., 2012). Phytochrome B (phyB) plays an important role in red light-induced stomatal development. Loss of *phyB* function prevents this increased production of stomata under high intensity red light. phyB can also promote the expression of *FAMA* and *TMM* genes in young leaves (Casson et al., 2009). Consequently, phyB has a significant role in the mediation of epidermal cell division and stomatal development. PHYTOCHROME-INTERACTING FACTOR 4 (PIF4), a bHLH transcription factor, can be transported to the nucleus upon binding to

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phyB. PIF4 may also regulate stomatal development with SPCH, MUTE, and FAMA. Mutations of *PIF4* display a similar defect as in the absence of *phyB* (Casson et al., 2009).

Plasma membrane H^+-ATPase regulates blue light-induced stomatal opening. It is activated via a signaling mediator BLUE LIGHT SIGNALING1 (BLUS1) and blue light-receptor phototropins (phot1 and phot2). BLUS1 and phosphatase act as positive mediators between the H+-ATPase and the phots during stomatal opening. BLUE LIGHT-DEPENDENT H^+-ATPASE PHOSPHORYLATION (BHP) is a novel signaling regulator in blue light-induced stomatal opening interacting with BLUS1, which is owned by the MAPKKK family. Loss of *BHP* function results in impaired stomatal opening in response to blue light (Hayashi et al., 2017). The phots are light-induced receptor kinases, which mediate stomatal opening and phototropism. the *phot1 phot2* double mutant fails to show the blue light-induced stomatal opening and the H^+-ATPase activation, but *phot1* and *phot2* single mutants retain these responses (Doi et al., 2004). A recent study displayed that BLUS1 kinase is phosphorylated by phot1 and phot2, which acts as a common substrate in stomatal opening through the activation of the plasma membrane H^+-ATPase via phosphatase (Takemiya and Shimazaki, 2016).

The light-induced stomatal opening is also inhibited by Rho-type (ROP) GTPase 2 (ROP2). ROP-interactive Cdc42- and Rac-interactive binding motif-containing protein 7 (RIC7) interacts ROP2 and mediates downstream processes. Loss of *RIC7* function activates light-induced stomatal opening, while overexpression of *RIC7* represses light-induced stomatal opening. RIC7 interacts also with Exocyst subunit Exo70 family protein B1 (Exo70B1), a positive regulator of stomatal opening, to optimize the extent of stomatal opening by inhibiting the function of Exo70B1. The mutant *exo70b1* and double mutant *ric7*/*exo70b1* both display inhibited light-induced stomatal opening (Hong et al., 2016). ENHANCED RESPONSE TO ABA 1 (ERA1) encodes the farnesyl transferase β subunit, which dominates stomatal closure in plants. Loss of *ERA1* function results in more closed stomata phenotype. Further studies indicated that *era1* mutants shows impaired blue light-induced stomatal opening, which suggested a potential function for ERA1 farnesylation in blue light-induced stomatal opening (Jalakas et al., 2017). In addition, Photosystem II Subunit S (PsbS), a integral membrane protein, affects a chloroplastderived signal for light-induced stomatal opening. Over-expression of *PsbS* results in impaired light-induced stomatal opening and a 25% reduction in water loss per CO_2 assimilated under field conditions (Głowacka et al., 2018).

Synergy effects of light and CO_2

The stomatal opening is mediated by light and low concentrations of CO_2 with synergy effects. CONVERGENCE OF BLUE LIGHT AND CO2 1/2 (CBC1/CBC2) are protein kinases related to blue light, which redundantly promote stomatal opening in response to both blue light and low concentrations of CO_2. It was suggested that CBCs positively mediate stomatal aperture by integrating signals from blue light and low CO_2 (Hiyama et al., 2017). In contrast to blue light-induced stomatal opening, the viewpoints about red light-induced stomatal opening are controversial. Some studies showed that red light-induced stomatal opening may be resulted in a low intercellular concentration of CO_2 brought about by mesophyll photosynthesis (Horrer et al., 2016) However, other investigators suggested that such a reduction in the intercellular concentration of CO_2 of leaves was insufficient to lead to stomatal opening. Hiyama et al. (2017) speculated that

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the reduced intercellular concentration of CO_2 might result in stomatal opening by inhibiting the S-type channels through CBCs, but such a response did not display in the *cbc* mutants. Further study is needed to elucidate the role of CBCs in red light-induced stomatal opening.

Temperature and air humidity

Temperature affects stomatal development in a complex manner. Temperature increases often leads to somatal opening, whereas heat stress often promptly mediates stomatal closure to decrease transpirational water loss in some plant species (Lahr et al., 2015). Increased temperature restrains the expression of SPCH that acts as the major mediator of stomatal lineage initiation (Vatén et al., 2018). PIF4 is also a core component of high-temperature signaling, which accumulates in the stomatal precursors and combines with the promoter of SPCH in increased temperature. In addition, PIF4 represses also SPCH activation and stomatal production. This study proposed a model where warm-temperature-activated PIF4 binds and represses SPCH expression to restrict stomatal production at increased temperatures (Lau et al., 2018). The CO_2-induced variations of stomatal closure associates with heat stress tolerance. The eCO_2 moderates the negative effects of heat stress, which is accompanied by greater amounts of *RESPIRATORY BURST OXIDASE 1* (*RBOH1*) transcripts and decreased stomatal aperture. Loss of *RBOH1* function results in the impaired eCO_2-induced stomatal closure and the compromised eCO_2-enhanced water use efficiency as well as the heat tolerance (Zhang et al., 2018).

Stomatal movement is influenced by relative air humidity (RH) with ABA content. High elevated air movement (MOV) reduced length and aperture of stomata in plants developed at high RH and increased stomatal sensitivity to ABA (Carvalho et al., 2015). In this process, *CYP707A1*, a ABA catabolism gene, plays a prominent role for influencing stomata development and ABA content. Over-expression of *CYP707A1* during dark in high RH reduced the ABA content in the guard cells and prevented stomatal closure, whereas loss of CYP707A1 gene function resulted in reduced stomatal aperture (Arve et al., 2015; Jalakas et al., 2018). Compared with the influence of CO_2 and light on stomatal development, the molecular mechanisms underlying the action of temperature and air humidity on stomatal development should be further and deeper to study.

The influence of plant hormones

Some hormones, such as Abscisic acid (ABA), jasmonate (MeJA), Brassinosteroids (BRs), Strigolactones (SLs), Salicylic acid (SA) etc. have a strong correlation with stomatal development. With the mechanism of stomatal development being studied in the past decade, many researches have opened the door to understand the function of plant hormone in stomatal development.

Role of ABA

ABA is well known to mediate the opening and closing of stomata in response to changes in water balance. ABA levels are low in the Arabidopsis *aba2* mutant, with the mutant displaying high stomatal density. ABA INSENSITIVE 1 and ABA INSENSITIVE 2 (ABI1 and ABI2) are protein phosphatase 2C proteins, which regulate

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ABA-mediated stomatal closure interacting with protein kinases OST1 (Tanaka et al., 2013). The pathway for ABA-mediated stomatal closure is related to perception of ABA that results in the activation of guard cell anion channels by OST1. Loss of *OST1* function results in insensitivity to ABA-mediated stomatal closure and opening, which indicates that OST1 is a positive regulator in ABA signaling (Mustilli et al., 2002; Acharya et al., 2013). OST1 needs normal ABI1 function for its ABA-dependent activation and interacts directly with ABI1 protein (Park et al., 2009). In addition, ABA-induced stomatal closing are abolished in *abi1* and *abi2* mutants (Pei et al., 1997). Although ABA interacts with different functional proteins, transcription factors, kinases, and various environmental factors, the molecular mechanisms about these interaction are massively complex and are not entirely clear.

Role of MeJA

The exogenous MeJA can reduce the stomatal index and stomata density on the cotyledons of Arabidopsis. Coronatine (COR) is perceived via a receptor complex formed by CORONATINEINSENSITIVE 1 (COI1) and JASMONATE ZIM DOMAIN (JAZ) proteins, which promotes entry of bacteria into the plant apoplast by facilitating stomata opening (Yan et al., 2009). COR and jasmonate isoleucine (JA-Ile) co-receptor JAZ2 modulates stomatal aperture by the signaling module COI1-JAZ2-MYC2,3,4-ANAC19,55,72 during bacterial invasion. The jaz2 mutant shows partially repressed pathogen-induced stomatal closing, which is more sensitive to Pseudomonas. The JAZ2 binds to the MYC transcription factors directly mediate the expression of ANAC19,55,72 to control stomata aperture (Gimenez-Ibanez et al., 2017). In addition, the MYC transcription factors negatively modulate jasmonate-inhibited stomatal development and act upstream of the SPCH and FAMA to regulate stomatal development. The stomatal development of the *myc2 myc3 myc4* triple mutant is insensitive to MeJA treatment (Han et al., 2018).

Role of BRs

BRs are steroid hormone that promotes stomatal closure in an ABA-independent manner (Kim et al., 2012). BRASSINOSTEROID INSENSITIVE2(BIN2), a important regulator in BR signaling, encode a glycogen synthase kinase 3 (GSK3)-like kinase (He et al., 2002). BRs negatively modulate stomatal development by repressing BIN2 kinase-induced inhibition of YDA. BIN2 phosphorylates and inactivates the YDA, which inhibits stomata formation. Overexpression of *BIN2* displays a similar stomatal overproduction phenotype as *bsu* mutants. Besides, BRs have been directly involved in stimulating stomatal development in hypocotyls through BIN2 phosphorylation and inactivation of SPCH, which acts downstream of the MAPKs and stimulates cell division and stomatal development. BRASSINOSTEROID-INSENSITIVE 1 (BRI1) kinase binding with BR recruits BRI1-ASSOCIATED RECEPTOR KINASE 1 (BAK1) to produce a receptor complex on plasma membranes (Shang et al., 2016). Transphosphorylation between BRI1 and BAK1 further enlarges BRI1 and BAK1 kinase activities, which results in inactivation of BIN2 by the upstream phosphatase BRI SUPPRESSOR1(BSU1) under high BR levels (Zhu et al., 2013). Loss of *BSU1* function results in massive stomata formation, which needs BIN2 activity (Kim et al., 2012). Loss of *BAK1* function results in insensitivity of ABA-mediated stomatal closure and inhibition of OST1 expression and ROS production. It was further indicated that

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BAK1 interacts with OST1 near the plasma membrane, which increases sensitivity in response to ABA. In addition, ABI1 interacts with BAK1 and impairs the interaction of BAK1 and OST1 (Shang et al., 2016).

Role of SLs

SLs play a vital role in regulating stomatal closure in an ABA-independent mechanism. SLs promotes a significant increase in H_2O_2 and NO contents, which is needed for stomatal closure. Disruption of MORE AXILLARY GROWTH 2 (MAX2), DWARF14 (D14), and SLAC1 represses SL-induced stomatal closure. Loss of MAX2 function leads to increased stomatal conductance and more widely opening stomata (Piisilä et al., 2015). The *slac1* mutant shows compromised SL-mediated stomatal closure, showing that SLAC1 is necessary for SL-mediated stomatal closure. Although SL-induced stomatal closure requires H_2O_2, NO, and SLAC1, the detailed molecular mechanism by if SLs regulate the stomatal response remains unknown. It will be required to study whether H_2O_2-activated Ca^{2+} channels are also needed for SL-induced stomatal closure (Lv et al., 2018).

Role of SA

SA regulates ROS production in guard cells through peroxidase-catalyzed reaction, leading to stomatal closure. AtSIZ1 is a small ubiquitin-like modifier (SUMO) E3 ligase, which negatively mediates stomatal apertures via the SA-triggered ROS accumulation. Loss of AtSIZ1 function leads to the accumulation of endogenous SA, which enhances the production of ROS mediated by salicylhydroxamic acid (SHAM)-sensitive peroxidases and impairs stomatal aperture (Miura et al., 2013). In addition, plants growing in the ethylene precursor 1-aminocyclopropane-1-carboxylic acid display increased stomatal density. Stomatal division and development is enhanced in cucumber hypocotyls after brief treatment with ethylene. Furthermore, auxin and gibberellin modulate stomatal aperture opening and closing (Saibo et al., 2003). Compared with other molecular regulatory pathways, the molecular mechanisms underlying the action of ABA and other hormones on stomatal development have not been clearly established.

Future directions

Stomata enable plants to regulate the entry of CO_2 assimilated in photosynthesis and adjust evaporation of water. Although some underlying mechanisms and genes related to stomatal development have been studied, many complex questions related to stomatal morphogenesis and division are still largely unanswered. Future research should involve bioinformatics mining of published gene data, information analysis of transcriptomic and proteomic for deeply studying stomatal development and guard cell responses to environmental factors. In addition, very little is known about the underlying molecular basis for the changes of hormonal factors such as ABA, ethylene, auxin, and gibberellin. The mechanism and regulatory pathway controlling variation in stomatal development in response to environmental signals such as photoreceptors, temperature, and humidity is uncertain. Other problems include determining the genes and pathways involved in stomatal development, ascertaining whether the molecular mechanism of stomatal development differs between monocotyledons and dicotyledons, and understanding how

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intercellular signaling is superimposed and orients the intrinsic polarity. Finally, how environmental signals modulate stomatal development needs to be elucidated. Many questions thus remain to be addressed. In a word, the genetic network for the regulation of stomatal development is too complex and tightly impacted by both intrinsic and external signals. The exact molecular mechanisms underlying the interactions among the various impact factors and environmental signals during stomatal development deserve further investigation.

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