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Review Article

Stomatal Development and Impact of Stomatal Movement on Secondary Metabolism in Medicinal Plants

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Abstract

Stomata are minute microscopic pores found in the epidermis of the aerial parts of plants and reported to be present about 400 million years ago in the earth eco-system. They serve as a gate way of gaseous exchange in plant on which the whole world depends to get oxygen to breathe. In this review efforts have been made to discuss process of stomatal development and its control by a genetic tool box comprising of many genes and signalling cascades. There is discussion on interlinking of genes to formation of stomata in strict control of relevant genes. Identity of cells, asymmetric cell division, stomatal density, patterning and clustering are discussed with respect to signals coming from environment and or the hormonal cascade. Fate of absorbed light energy in green plants is briefed and stomatal opening and closing mechanism under initial and mild stress conditions which shifts primary metabolism to the secondary metabolism resulting in increased secondary metabolites production is highlighted. Impact of disrupted membrane integrity and permanent damage to photosystem II on growth in plants under prolonged and severe stress conditions is elaborated. In nature, plants have different pheno-phase, life span, preferred growth season, soil type and climatic requirements. Duration and intensity of stress at different phenol-phase may have different impacts on secondary and primary metabolism. Focusing particularly on medicinal plants, we explained how difficult is to define a hypothetically optimum stress condition which cause increase in secondary metabolites without significantly compromising the potential biological yield. Studies on crop specific responses to stress of various intensities and duration imposed at different pheno-phases are required to be conducted that may further help in explaining the optimum stress conditions in medicinal plants.

ABBREVIATIONS

ABA- Abscisic acid, **ACD**- Asymmetric cell division, **ARF5**- Auxin response factor 5, **ARR16**- ARABIDOPSIS RESPONSE REGULATOR16, **AUX**- Auxins, **AXR3-** Auxin resistant 3, **BASL**- Breaking of asymmetry in the stomatal lineage, **B-GATA**- Gata factors of B-subfamily, **bHLH**- basic helix-loop-helix, **bHLH-LZ**- bHLH-leucine zipper, **BIN 2**- Brinsensitive 2, **BR**- Brassinosteroids, **CAM**- Crassulacean Acid Metabolism pathway, **CK**- Cytokinin, **CLA**- Constant light absorption, CLE9/10- CLAVATA3/ EMBRYO SURROUNDING REGION RELATED 9/10, **CLF**- CURLY LEAF , **COP1**- Constitutive photomorphogenic 1, **CRSP**- CO_2 responsive secreted protease, **DM**- Dna methylation, **EPF1**- EPIDERMAL PATTERNING FACTOR 1, **EPFL9**- Epidermal patterning factor like 9, **ER**- Erecta, **ERf**- The erecta family, **ERL1**- Erecta like1, **ERL2**- Erecta like 2, **FLP**- FOUR LIPS, **FMA**- Fama, **GCs**- Guard cells, **GMCs**- Guard mother cells, **GSK3**- Glycogen synthase kinase 3, **GSL8/CHORUS**- GLUCAN SYNTHASE-LIKE 8, **H3K27me3**- Histone3 K27 trimethylation, **HDG2**- HOMEODOMAIN GLABROUS2, HD-ZIP IV The homeodomain leucine zipper class IV, **HM**- Histone modification, **HSL1**- HAESA-LIKE 1, **ICE1**- INDUCER OF CBF EXPRESSION1, **IDD16**- Indeterminate domain family 16,**JA** – Jasmonates, **LRR-RLKs**- Leucine-rich repeat-receptor-like kinases, **MAPKKK**- Mitogen-activated protein kinase kinase kinase, **ML1**- MERISTEM LAYER 1, **MMCs**- Meristemoid mother cells, **MP**- Monopteros, **MPK 3/6**- Mitogen activated protein kinase 3/6, **MYB88**- Myeloblastosis 88, **NADP**- Nicotinamide-adenine dinucleotide phosphate, **NPC**- Other normal physiological conditions (absence of stress), **NPQ**- Non-photochemical quenching, **PAR**- Photosynthetically active radiation, **PC**- Pavement cell, **PHPB**- Plant and human pathogenic bacteria, **PIF4**- Phytochrome interacting factor 4, **PRC2**- Polycomb Repressive Complex 2, **Pst**- P. syringae pv. Tomato, **RBR**- Retinoblastoma related, **RdDM**- Rna directed dna methylation, **SCRMs**- Scream, **SD**- Stomatal density, **SDD1**- Stomatal density and distribution, **SERKs**- Somatic embryogenesis receptor kinases, **SI**- Stomatal index, **SIS**- Stoma-in-Stoma, **SLGC**- Stomatal Lineage Ground Cell, **SPCH**- Speechless, **TMM**- Too many mouths, **YDA- MAPK- YODA**-Mitogen-Activated Protein Kinase, YDA- YODA

INTRODUCTION

The photosynthesis is performed by green plant in presence of sunlight thereby fixing of atmospheric CO_2 into glucose and as a by-product, oxygen is evolved and released into the atmosphere through stomata located on surface of the plant parts. These stomata which are indeed the gate way to the life on earth, are minute microscopic pores found within the epidermis of the aerial parts of plants. "Stoma" (singular) has been coined from the Greek word which means "mouth." Stomata have a critical role as

regulator of gas exchange and water loss between the plant and the environment. They are located in majority of aerial parts that includes cotyledons, leaves, stems, petals, sepals, stamens and gynoecia. It is also present in some surfaces of developing fruits (e.g. example, apple, banana, grape & tomato). In majority of herbaceous plants, stomata are found on both the upper (adaxial) and the lower (abaxial) epidermis of leaves, but with varying densities. Dicotyledonous leaves have less stomata within the upside portion [1]. Stomata are formed by a pair of specialised guard cells and altogether, the pore, the guard cells; additionally adjacent subsidiary cells are called the stomatal complex.

Stomata enables the entry of CO_2, necessary for photosynthesis, release of oxygen and loss of vapour which is important for the regulation of leaf temperature and solute transport [2]. Stomata within the Plantae Kingdom probably appeared as a necessity for the transition of plants from their aquatic habitat to terrestrial land. Stomatal opening and shutting are often regulated by the plant in response to the environmental conditions [3]. Synchronization of opening and closing of stomatal pore is governed by hydrostatic pressure in guard cells. Stomata regulates the photosynthesis and the transpiration; the two major and very important physiological processes within the plant. Besides regulating internal temperatures, it also acts as a crucial site of plant defence and entry of pathogen [4]. Stomatal guard cells are highly specialized in function in maintaining optimal pore size to sustain optimum gaseous exchange in relation to surrounding conditions. Sensitivity and continuous response to diverse range of stimuli in autonomous manner has been reported. This special character constitutes a vital model system for environmental and endogenous signal transduction in plants [5].

Stomatal size, shape, density (SD), index (SI) and patterning vary among different plant species. The Stomatal patterning is the property of the species and it varies considerably. In most monocotyledons and gymnosperms, they are found in rows along the length of the leaf. In *cress plant*, they're found evenly spaced and almost never next to each other with a minimum of single cell between two stomata called one-cell-spacing rule [2]. Clustering of stomata in the form of groups of two or more stomata with direct contact has been reported in a few plant species [6].

There are two basic forms of stomata anatomically, one with kidney-shaped-guard cells and elliptical stomata, just like the ones in *cress;* and the other with dumb-bell-shaped guard cells restricted to the monocotyledons. Arabidopsis stomatal complexes is classified as anisocytic or cruciferous type in which the guard cells are encircled by three unequal size subsidiary cells obtained from two asymmetric divisions [7]. Stomatal morphogenesis and behaviour are controlled by environmental factors such as quantity as well as quality of light, availability of water and atmospheric humidity, temperature, CO_2 concentrations, hormones (abscisic acid, cytokinins, auxins etc), mineral nutrition, circadian rhythms, life cycle of the leaves, and gaseous environmental pollutants among others [3].

A number of reports have appeared during the last decade on understanding of the genetic regulation of stomatal development. Stomata are formed by a series of asymmetric cell divisions and a genetic toolbox has been identified that tightly controls its development and patterning using the *mouse-ear cress* as a model system. Several mutations affecting guard cells were studied after the primary report of TMM (too many mouths) mutation causing stomatal clusters during mid 1990s [8]. The alteration within the normal number, pattern, particular and distribution of stomata within the mutants has allowed an understanding of how concerned genes control stomatal formation. Study of formation of the stomatal complex presents a unique opportunity to understand the control of cell polarity and asymmetric divisions in plant cells [3, 9]. The knowledge so far about guard cells reveals their complexity and hence, deeper understanding of stomata may allow human regulation of stomatal morphogenesis and behaviour, resulting in improvement in crop productivity and stress tolerance [2].

BACKGROUND

Stomata played pivotal role in development of earth eco-system since 400 million years, as the primitive fossil with noticeable stomata and vascular tissue were reported in remains of vascular plant of extinct genus *Cooksinia* dating back 418 million years ago. This plant marks the origin of new approach of plant based life occupying terrestrial habitat by consuming water and nutrients obtained from land [10, 11]. Reported for Cooksonioids to have barely more than three stomata, assembled around the bottom of reproductive sporangium with an evidence that the main sporophyte axes of these plants were incompetent of autonomous photosynthesis based on their anatomy. Frequency and positioning of stomata of earliest fossil of hornwort and moss suggests that ancestral stomata did not execute a role in photosynthetic gas exchange when there was a very high concentration of CO_2 in the air as the stomatal pore was formed and remained open.

The SD was low in ancient terrestrial plants surrounded by very high CO_2 concentration and during evolutionary years, the SD increased with decrease in aerial CO_2 concentration. The present complex stomatal assembly is probably forwarded by considerable alteration, recruiting nearby subsidiary cells which facilitate in opening or closing of stomata, re-locating of stomatal complexes beneath protecting epidermal cells and incorporating manifold asymmetric divisions in precursors by creating diversity of stomatal distributions [9]. Bryophytes are a basal terrestrial plant group, comprises of liverworts, mosses and hornworts. Liverworts are devoid of stomata and the gas exchange is carried out by epidermal air pores; whose structure, development and morphology vary from stomata. The mosses and hornworts possess stomata, which is indicative on the probability of liverworts being diverged from other bryophytes before the genesis of stomata.

In the angiosperm, there exists a committed epidermal lineage which produces stomata. By studying existing patterns and development in stomata of angiospermic plants, one can wonder about their genesis. In simple ontogenesis observed in few mosses, the development of stomata occurs in one asymmetric cell splitting straight in production of a GMC. In *Funaria hygrometrica*, incomplete division of GMC occurs,

wherein the nuclei of two guard cell are partitioned through an incomplete cell wall [12]. In case of *Polytrichastrum formosum* there is break of specificity rule and stomata occasionally are formed adjacent to one another [13].

In case of mosses, diversified structures of stomata are observed and many moss do not possess stomata as the activity of stomata is different in these plants. Sphagnum possesses pseudostomata that aids in desiccation of spore instead of acquiring CO_2 [14]. There appears amplifying divisions in case of ferns that suggest unusual mechanism for regulation of number of cell and density of stomata and formation of specialized subsidiary cells. In this case prior to differentiation into a GMC, an epidermal cell splits into one to two asymmetric cell divisions [13].

In Gymnosperms like pines, subsidiary cells are produced from meristemoidic splitting or splitting of protodermal cells lying adjacent to stomata, or subsequently both. In case of *Pinus strobus/banksiana*, meristemoids split only once symmetrically to produce a GMC and a subsidiary cell and this subsidiary cell and adjacent epidermal cell amplify in terminal manner over GMC (*Pinus strobus/banksiana*, meristemoids split only once symmetrically to produce a GMC [13]. Consequently, GMC and afterwards the guard cell combines, shielded by assembly of epidermal subsidiary cells of merged genesis and associated to hypodermal subsidiary cells. In *Cacti* which follow CAM i.e., Crassulacean Acid Metabolism pathway, stomata open only during dark so as to prevent loss of water. Stomataless species are thus smaller and occur only during unfavourable growth conditions.

In monocotyledons a powerful base to tip inclination for differentiation of leaf with cell producing stomata lineages formed at the bottom of leaf is reported. Without any previous shift from a self renewing meristemoid stage, asymmetrically dividing cell produce GMCs. Protodermal cells connecting GMC differentiate as regards to GMC and by dividing asymmetrically produce subsidiary cells. Later, GMC splits to form guard cells which possess unusual flat or dumbbell shaped structure. In Tradescantia, entire stomatal patterning could be re-explored during which GMCs changes their fate and are differentiated into the epidermal cells.

Process of Stomatal Formation in Dicotyledon Plants

Out of three rules followed for stomatal development, the first is the series of asymmetric cell division, the second is proper patterning to separate stomata by placing a non stomata cell between two stomata, and the third is maintenance of proportion of the stomata and non-stomatal epidermal cells which is governed by environment factors [14]. In dicotyledons plants, development like the one used as research model i.e., Arabidopsis, lineages are originated from different sites located on leaf. The series of these processes starts with the subset of protodermal cells to get developed into Meristemoid Mother Cell (MMC). In the following developmental processes are an asymmetric division forming two daughter cells of unequal size, a meristemoid; a small triangular cell and Stomatal Lineage Ground Cell (SLGC), which is a larger cell. The SLGC can follow three different paths; it might become an MMC, might differentiate into a Pavement Cell (PC), or it might divide to produce two cells which may independently take one amongst these three options. The character like stem cell exists in every meristemoids including primary and satellite. The meristemoid produced in this way has stem-cell character; undergoes 1-3 asymmetric divisions; then has two choices. It can stay as a MMC (like its parent) or undergoes a second change in nature to become a "Guard Mother Cell" (GMC). The major characteristic of a GMC is that it undergoes a symmetric division to produce two equal daughter cells which undergo a tertiary state transition to become mature guard cells. The neighbouring cells can render mechanical support and supply ions needed for movement of guard cell. Subsidiary hiring, amplifying and spacing divisions need cell to cell communication and they all in reciprocation contribute in patterning. It is possible that the frequency, with which cells involve in this partition, can be manipulated in nature to produce extraordinary variation of stomatal patterns. The divisions occurring in meristemoid is known as amplifying divisions which might occur till quarter times. Regeneration of every division leads to rise in meristemoid or amplification of total number of SLGCs that are formed by solitary origin. Meristemoids transformed into GMC followed by specific changes in morphological characteristic proceeds for one time symmetric division (Figure 1).

Major Genes Involved in Stomata Formation

The Stomatal Density and Distribution (SDD), encodes a subtilisin-like Ser protease, thought to be involved in signalling pathways that regulate the guard cell lineage [15]. It regulates entry of the cells into the stomatal lineage, the quantity, frequency and orientation of asymmetric divisions [16]. ERECTA (ER), and its two closely related paralogues ERL1 and ERL2 consists of ER, ERL1, and ERL2. ER as well as its functional paralogues, ERL1 and ERL2 code for leucine-rich repeat-receptor-like kinases (LRR-RLKs), [17]. These proteins work in unison within the regulation of stomatal patterning besides promoting organ growth [18] and coordination of proliferative division of cell within the cortex [19]. TOO MANY MOUTHS (TMM), gene product occurs to be a leucine-rich repeat-containing receptor-like protein and functions as a component of a signalling pathway that regulates stomatal patterning [2]. The tmm with recessive loss of function mutation leads to clustered and increased number of stomata. They are also involved in meristemoid activity regulation and accurate orientation of the asymmetric divisions necessary to form clusters [8]. YODA (YDA) codes for a mitogen-activated protein kinase kinase kinase (MAPKKK) which plays a crucial function in identity of guard cell and pattern. The yda give rise to an excessive quantity of cells to enter in to the stomatal pathway causing increased quantity of guard cell and clustering in cotyledons and hypocotyls. The down-regulation of YDA allows cells to enter in to the stomatal pathway [20]. Downstream of MITOGEN-ACTIVATED PROTEIN KINASE3 (MPK3), YODA as well as MPK6 and consequent upstream regulation of kinases like MKK5 as well as MKK4 form a module which interacts with YODA to form a MAPK signalling cascade that negatively controls the entry into the stomatal lineage [21]. FOUR LIPS (FLP) gene products are MYB124, a two-repeat (R2R3) MYB (myeloblastosis) protein expressed soon after the ultimate symmetric division that generates a pair of guard cells. FLP encompasses a paralogous gene, MYB88 having high sequence similarity and an overlapping

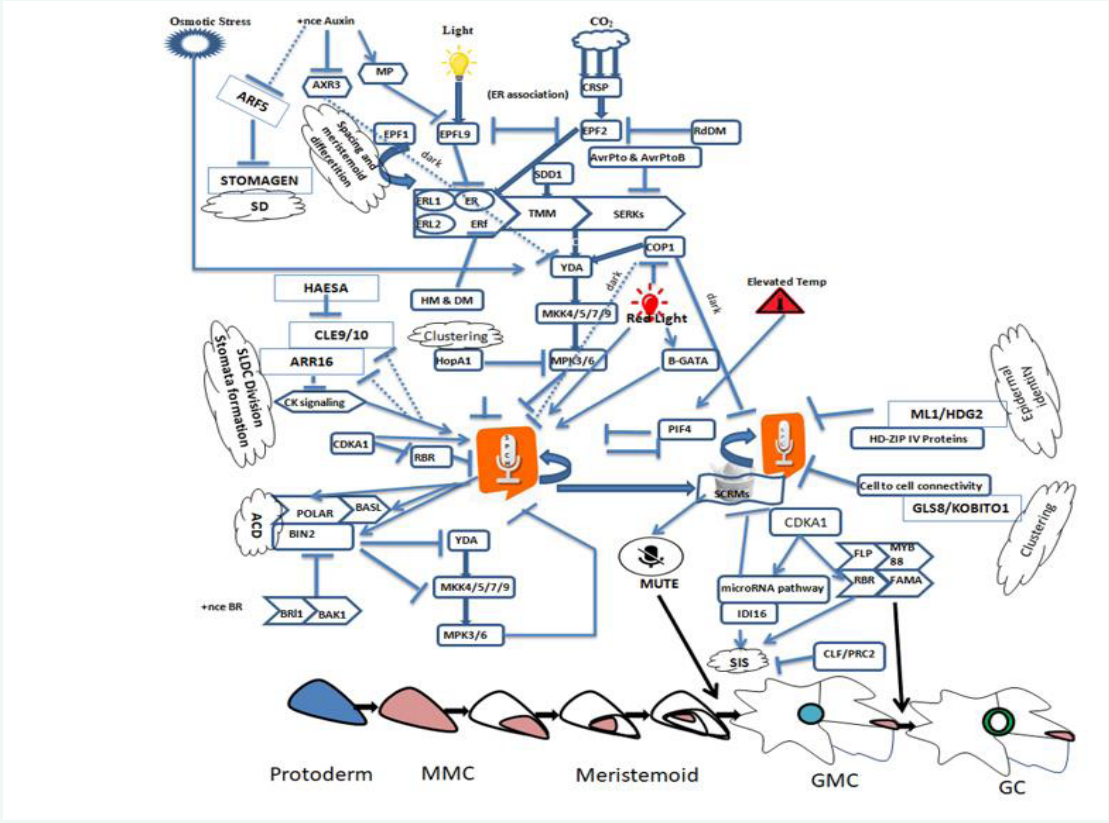

Figure 1 (a): Genetic tool box governing stomatal formation and (b) changes in the developmental stages of stomata in plants.
represent activation/enhance ⊥ represent inhibition or suppression
GMCs Guard mother cells, GCs Guard cells, MMCs Meristemoid mother cells, SCRMs Scream, MPK 3/6 Mitogen activated protein kinase 3/6, TMM Too many mouths, ERf the Erecta family, ER Erecta, ERL1 Erecta like 1, ERL2 Erecta like 2, SERKs Somatic embryogenesis receptor kinases, EPFL9 Epidermal patterning factor like 9, RdDM Rna directed dna methylation, HM Histone modification, DM Dna methylation, SDD1 Stomatal density and distribution, BIN 2 Brinsensitive 2, CK Cytokinin, PIF4 Phytochrome interacting factor 4, B-GATA Gata factors of B-subfamily, AXR3 Auxin resistant 3, COP1 Constitutive photomorphogenic 1, CRSP CO2 responsive secreted protease, BASL Breaking of asymmetry in the stomatal lineage, HD-ZIP IV The Homeodomain leucine zipper class IV, IDD16 Indeterminate domain family 16, RBR Retinoblastoma related, MYB88 Myeloblastosis 88, SPCH Speechless, FMA Fama, MP Monopteros.

function with FLP. Both together restrict the quantity of divisions within the last stage of the stomatal lineage [22]. In the flp phenotype the one-cell-spacing rule is not followed. Without affecting meristemoid production or activity, the flp regulates production of guard cells shows that it's regulation takes place between the cell cycle and cell specification [2, 8].

SPEECHLESS (SPCH), MUTE and FAMA (FMA)

Three closely related paralogous genes SPCH, MUTE and FAMA codes for basic Helix-Loop-Helix (bHLH) transcription factors needed for the development of stomata. Increase in functional mutation in any of these paralogous genes, it might lead to conditions causing lack of stomata. Expression analysis and mutant phenotype studies revealed that these genes help in regulation of key cell-state transitions that result into the formation of guard cell [23]. SPCH is needed for performing the primary asymmetric division in the stomatal pathway. The gene is expressed within the developing epidermis and is required for expression of MUTE and FAMA [24]. When there is MUTE loss of function mutant, it completely lacks stomata. Meristemoids undergo excess of asymmetric divisions which creates an epidermis with arrested meristemoids surrounded by rosette patterns. Various studies reveal MUTE instructs in the key transition from the meristemoid cell fate to the guard mother cell fate [25]. FAMA, like MYB88 and FLP, possess a crucial role in regulating divisions at the end of the stomatal pathway, but it also enhances the fate of guard cell. When there is a mutation in FAMA, the fama-1 mutants exhibit absence of stomata and there also occurs presence of clusters of tiny cells in place of stomata. These clusters are termed as fama tumors. This phenotype and other FAMA studies suggest that GMC undergoes excess of symmetric divisions which fails to differentiate into the mature guard cells [24]. Three bHLH proteins form a three-step transcriptional pathway which helps in governing key cell state transitions in case of stomatal pathway. The SPCH aids in regulation of the entry into the lineage as well as the transition from MMC to meristemoid. The MUTE aids upon the change in meristemoid state to GMC state. Finally, the FAMA takes care of the ultimate decision of the GMC state to differentiate into guard cells state [23]. The mechanism of SPCH, MUTE, and FAMA coordination was completely unknown in the recent past. Discovery of other two bHLH proteins involved into the differentiation of stomata,

the SCREAM (SCRM) as well as the SCRM2, unravelled the hidden coordination of SPCH, MUTE, and FAMA in stomatal development and differentiation. The SCRM is ICE1, a kind of transcriptional regulator of cold tolerance, that suggests a possible link between the environmental as well as the developmental programs [26]. The SPCH decides the entry within stomatal lineage and integrates various environmental as well as the developmental signals coming from various cascades namely YDA-MKK4/5/7/9, BIN2, B-GATA, CDKA1 along with PIF4. SPCH is also involved in regulating the cell division occuring in asymmetric way, in case of the stomatal lineage, by the activation of the transcription of the two major distinct proteins namely BASL as well as POLAR. Cell-to-cell connectivity, HD-ZIP IV proteins, IDD16, microRNA pathway along with RBR enacts in conjugation with spatio temporal regulation of expression of SPCH. The SPCH accelerates it's own activity by self activation as well as activation of SCRMs and hence, there is sustainance of meristemoid as well as MMC cell fate. Further, there is inhibition of it's own self on activation by the EPF2-TMM cascade calrifying it's role in stomatal patterning as well as distribution [27].

A Stomatal Patterning Model

Control of stomatal development can be explained at molecular level by following the model plant Arabidopsis [13]. There is a genetic toolbox regulating to development of stomata as well as patterning in Arabidopsis. At the central position of this genetic toolbox are bHLH (Basic helix-loop-helix) transcription factors like SPCH (SPEECHLESS) and SCRMs (ICE/SCREAMs) however, the MUTE and FAMA are also key players. All the key players aid in formation of stomata, and are controlled by signals received directly or through YDA-MAPK Cascade [4]. Three important functions carried out by these genes are i) the initiation and entry in the stomatal lineage is carried out by SPCH ii) execution of asymmetric division of precursor stomatal cells by MUTE and promotion of differentiation of guard cell by FAMA [28].

To organize stomatal distribution, cells communicate by exchange of positional information, directing the placement of stomata and also of the development of subsequent one so developed. A straightforward model that unifies several genes involved in stomatal pattern formation would be that of SDD1 which activates an unknown ligand that binds to TMM receptor. TMM interacts with the ER family thus the signal is passed on across the YODA-Mitogen-Activated Protein Kinase (YDA- MAPK) signalling pathway [29]. This includes EPIDERMAL PATTERNING FACTOR 1 (EPF1), a secretory peptide, initially thought to function as ligand for TMM after cleavage and activation by SDD1. The studies suggest that EPF1 could also be a positional cue for the TMM and ERECTA receptors. They are upstream of YDA, TMM, and ER family genes; however, they have been shown to be independent from SDD1, whose ligand remains unknown. A second secreted peptide, EPF2, has also been discovered. While EPF1 regulates stomatal patterning, EPF2 is assumed to control stomatal density [30]. The genetic regulation of the stomatal pathway has been studied in-depth during the last decade and several genes involved within the differentiation and patterning of stomata were discovered. Recently published studies have clarified the genetic regulation of stomatal patterning and the role of SPCH-SCRM co-ordination being pivotal in stomatal development [27].

Interlinkig Components of the Genetic Tool Box Controlling Stomatal Development in Plants

Three closely related paralogous genes SPCH, MUTE and FAMA encoding basic Helix-Loop-Helix (bHLH) transcription factors are needed for the development of stomata (Figure 1). At molecular level, the SPCH plays a central role in the genetic toolbox controlling formation and development of stomata in plants. It is vested with power to play a crucial role in the process of specification of the stomatal cell fate. It is the ultimate gene receiving hormonal and non hormaonal signals through different signalling cascade and further conveys and controlls the SCRMS. When there occurs loss of function mutation in any of these paralogous genes, it causes a condition in which there is lack of stomata. Expression analysis and mutant phenotype studies reveal that these genes help in regulation of key cell-state transitions that resulted into the formation of guard cell [23].

The SPCH is crucial for stomatal lineage initiation and needed for performing the primary asymmetric division because loss of function mutation of spch-1 in epidermal cells prevents asymmetric entry division and SPCH when over expressed caused ectopic entry division in the epidermis [24, 25]. Though transcribed in epidermal cells, the protein encoded by this gene is present in MMCs and meristemoids only and hence, the activity of this gene seems to be regulated at posttranslational level [24]. Downstream next important genes are INDUCER OF CBF EXPRESSION1 (ICE1) and SCREAM2 (SCRM2), both belong to homologous bHLH-leucine zipper (bHLH-LZ) transcription factors and a complete failure of stomatal formation is observed when ICE1 and SCREAM2 (SCRM2) are knocked out [26]. Heterodimerization of SPCH, MUTE, and FAMA with SCRMs (ICE1 and SCRM2) is required to trigger the successive MMC-meristemoid-GMC-GC fate transition [26]. The SPCH and ICE1/SCRM2 can directly target their own self and SPCH also targets ICE1/SCRM2 and by targeting their own promoters and thereby enhancing self-expression. They create a positive feedback loop needed to maintain the fate of MMC and meristemoid [31]. Studying the mechanism in *Brachypodium distachyon* and *Oryza sativa*, it was found that inactivation of either of the SPCH and ICE1 eliminated stomata which is indicative in monocots, the heterodimer of SPCH/ICE1 also functions as a switch for the stomatal initiation [32, 33].

Monitoring Cell Identity

To establish and maintain epidermal identity, a cell needs functions of MERISTEM LAYER 1 (ML1) and HOMEODOMAIN GLABROUS2 (HDG2) genes belonging to the HOMEODOMAIN LEUCINE ZIPPER CLASS IV (HD-ZIP IV) family genes [34,35]. Plasmodesmatal permeability and cellular integrity in the epidermis confines SPCH to stomatal lineage cells during stomatal development. Cellular integrity is disrupted or plasmodesmata permeability is increased due to mutation in callose synthase GLUCAN SYNTHASE-LIKE 8 (GSL8/CHORUS) or the glycosyltransferaselike protein KOBITO1. Results of such mutation facilitates intercellular movement of SPCH protein in the leaf epidermis, hence, disorganized cell divisions and

stomatal clusters are generated in the stomatal lineage [36, 37]. Controlling SPCH transcripts, a microRNA pathway is presumed to repress stomatal lineage initiation [38,39].

The SPCH transcription is also regulated by IDD16, a C2H2 zinc finger transcription factor from the INDETERMINATE DOMAIN (IDD) family and RETINOBLASTOMA RELATED (RBR). The RBR, targeted by CDKA;1 inhibits stomatal initiation by direct binding with SPCH to reduce SPCH expression [40,41]. Excess divisions in differentiated GCs and formation of the "Stoma-in-Stoma" (SIS) phenotype are results of downregulation of RBR in GMCs and GCs [42,43]. Identity of GC is maintained by Histone3 K27 trimethylation (H3K27me3) [44] and lesser availability of it causes SIS phenotype [42, 43]. However, the SIS phenotype are suppressed, if sufficient constitutive expression of CURLY LEAF (CLF) which is a member of Polycomb Repressive Complex 2 (PRC2) is made available as it works in H2K27me3 and other chromatin modifications [45]. Inhibition of GMC division occurs under interaction of RBR with PRC2, FAMA and FLP/MYB88 which redundantly functions with FAMA [44,46,47]. RBR and FAMA target the promoters of SPCH, EPF and FAMA [43].

Monitoring Asymmetric Cell Division

In the stomatal lineage, POLAR and BREAKING OF ASYMMETRY IN THE STOMATAL LINEAGE (BASL) are positively affected by SPCH. Both POLAR and BASL are polarized and located in periphery during the stomatal lineage Asymmetric Cell Division (ACD).The MAPK signaling is concentrated in cortex and segregated in SLGCs after ACD by BASL scaffold protein [48]. Phosphorylation and degradation of SPCH in SLGCs lead to differentiation of SLGCs into pavement cells however; stable SPCH expression under YDA-MPK3/6 signalling in meristemoids triggers the subsequent developmental processes [48]. The POLAR polarization requires BASL activity [49], and POLAR appears to function together with BASL to regulate the stomatal lineage ACD by confining BIN2 to the cell cortex [50]. The BASL activity is needed for polarization of POLAR [49] and by confining BIN2 to the cell cortex, POLAR and BASL work in association to monitor the stomatal lineage ACD [50].

Monitoring Stomatal Density and Patterning

Phosphorylation and further degradation of SPCH causes inhibition of its activity. Although there is a lack of report showing direct interaction of MPK3/6 and SPCH, the phosphorylation of SPCH is reported to be mediated by MPK3/6 [51] (Figure 1). In a recent study it has been found that ICE1/SCRM2 acts as a scaffolding partner for their interaction [52, 53]. The phosphorylation and degradation of ICE1/SCRM2 needs direct association with membrane bound protein kinase; MPK3/6 which is vital for the proper specification of the stomatal cell fate [53]. An MAPK cascade employing one YODA (YDA), four MAPKKs (MKK4/5/7/9) and two MAPKs (MPK3/6) has a direct association with SPCH•SCRM module development of stomata [20, 53, 54]. The YODA- MKK cascade receives signals from multiprotein receptor complex. This complex is made-up of leucine-rich repeat receptor-like protein TMM and ERECTA family (ERf); leucine-rich repeat receptor-like kinases ER, ERL1 and ERL2 as well as SOMATIC EMBRYOGENESIS RECEPTOR KINASEs (SERKs) [2,8,17,55,56].

These multiprotein complex receptors are equipped with indentification of some ligand proteins having cysteine-rich peptides of EPIDERMAL PATTERNING FACTOR-LIKE (EPFL) family. This identification is very much important as it becomes a switch between repression and promotion of development of stomata in particular regions [30,56,57,58,59,60,61,62]. The EPF1 and EPF2 have different mode of action. EPF1 depending on ERL1, warrant correct spacing and meristemoid differentiation [30,42]. EPF2 stimulate the downstream MAPK cascade and thereby represses initiation of stomatal lineage [44,57,60]. The RNA-directed DNA methylation (RdDM) is used to regulate EPF2, whereas histone modification and DNA methylation is used to regulate ERf genes [63]. EPFL9 participate with EPF2 without affecting the downstream MAPK response and in this way provides a positive association [44,60,61,64,65]. The hindrance of EPF2 is overcome by EPF9 [42].

Environmental Signals Monitoring Stomatal Development

Under osmotic stress conditions stomatal number decreased through down regulating SPCH protein level via MAPK-SPCH core developmental pathway [66]. PHYTOCHROME INTERACTING FACTOR 4 (PIF4) is accumulated in precursors of stomata under higher temperature stress. The PIF and the SPCH operate in negative feedback loop in that the SPCH protein inhibits PIF4 expression whereas the PIF4 can repress expression of SPCH by direct binding with the later [67]. Under exposure to red light stimulation, the GATA factors of the B-subfamily (B-GATA) transcription factors and the SPCH itself are over expressed. With direct binding to the promoter of the SPCH, B-GATAs aids in expression of express the SPCH under red light exposure [68]. Hormonal and environmental signals from the upstream signalling factors are ultimately accepted by SPCH.

Inhibition of RING E3 ubiquitin ligase CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1) promotes stomatal formation and this is carried out by multiple photoreceptors recognizing light signals [69]. All genes being operated upstream of YDA has a negative impact on stomatal development. The stomatal development is restricted by COP 1 in two ways either operating upstream of YDA and degrading SCRM proteins through ubiquitin/proteasome pathways particularly in dark conditions [70]. Stomatal density is increased under light irradiation due to positive impacts on expression of STOMAGEN [71]. Under elevated atmospheric carbon dioxide (CO_2) levels stomatal formation is repressed. This is because the positive effects of EPF2 is counteracted through cleavage of pro-peptide EPF2 by CO_2 RESPONSIVE SECRETED PROTEASE (CRSP) synthesized under conditions characterized by heavily elevated CO_2 [72].

For a plant infecting bacterium, the stomatal pores pave an entry point [73]. Inactivation of MPK3/6 by over expressed HopA1 under *Pseudomonas syringae* infection causes clustering of stomata [74]. In *Arabidopsis*, two effector proteins of *P. syringae* pv. tomato (Pst) AvrPto and AvrPtoB when over expressed, impacts positively on stomatal formation, probably through

impairing the function of their target SERKs, along with the ER-TMM complex [56].

Hormonal Signals Monitoring Stomotal Development

The Brassinosteroid (BR) intermediate namely the glycogen synthase kinase 3 (GSK3)-like kinase BRINSENSITIVE 2 (BIN2) can phophorylate SPCH directly. Additionally, because the BIN2 itself is a direct target of SPCH, such phosphorylation causes degradation of SPCH. Inactivation of BIN2 directly by the BR results in inhibition of stomatal formation in leaf epidermis. YDA controls MKK3/6 via MKK4/5/7/9. The MKK3/6 as well as the YDA is negatively controlled by BIN2 [74,75]. Though phosphorylation and degradation of SPCH is suppressed by BIN2, stomatal formation in hypocotyls is promoted by BR [76,77]. Cyclin- Dependent Kinases A;1 (CDKA;1) can also phosphrylate SPCH however, the phosphorylation of SPCH at serine 186 promotes stomatal initiation. It indicates that phosphorylation by multiple kinases in response to various signals are helpful in fine-tuning the activity and stability of SPCH [77].

Augmented level of Cytokinin (CK) or its signalling upholds expression of SPCH and in turn, the expression of the type-A ARABIDOPSIS RESPONSE REGULATOR16 (ARR16) and CLAVATA3/ EMBRYO SURROUNDING REGION RELATED 9/10 (CLE9/10) is induced by SPCH (Lau et al. 2014; Vaten et al. 2018). The CK regulates SLDC division and stomata formation through its direct impact on SPCH and negative dependency on ARR16. The CLE9/10 represses type-A ARRs (Figure 1). For establishing local domains of low CK signalling, both ARR16/17 and CLE9/10, counteracting each other, are essential and ultimately inhibits both SLGC division and stomatal formation [78]. The receptor kinase HAESA-LIKE 1 (HSL1) recognizes CLE9/10 peptides and thus, regulate the stomatal lineage cell division, the mechanism not known till date [79].

Auxin is another important plant hormone affecting stomatal development. It activates auxin response factor 5 (ARF5) and inhibits AUXIN RESISTANT3 (AXR3) and thus, negatively regulate stomatal formation. Expression of STOMAGEN in the mesophyll is inhibited by ARF5 whereas AXR3 operates upstream YDA MAPK cascade and promotes stomatal production in dark-grown seedlings [80,81,82].

Stress Impacts and Secondary Metabolism in Plants

When there are persistent changes in the environmental conditions, plants are susceptible to majority of abiotic stressess like drought, deficiency of nutrient, high and low intensity of light, ozone as well as UV-B radiation, salinity, low and high temperature and heavy metal toxicity. Abiotic stresses restrict growth and thus cause loss of production in terms of biological yield in plant. Figure 2 depicts three fates of light energy incident on PS II in a green plant. Utilization of the absorbed light energy occurs in competitive mode among i) photochemistry ii) dissipation of heat through non photochemical quenching and iii) reflecting back the light as chlorophyll fluorescence. The transport of electrons and protons from water to nicotinamide-adenine-dinucleotide-phosphate (NADP) and also in the phosphorylation of ADP to ATP is the main route through which the absorbed light energy is utilized. The energy in the form of electron may be used in defence mechanism by antioxidant enzymes activation to prevent stress impacts at cellular level [83].

During initial and mild stress conditions, the plant balances the osmotic conditions in cells and manages a suitable stomatal movements intended to fulfil CO_2 requirement through stomatal pores. During this stage, the PS II and membrane integrity are not permanently damaged and hence, the decline in growth is not significantly affected. In medicinal plants it is basically a kind of trade-off between two traits worth to understand is i) weakening primary metabolism as a sink leading to retarded growth and ii) strengthening secondary metabolism as a sink leading to increased yield of secondary metabolites. However, under prolonged severe stress conditions, a significant decrease in biomass and yield of seeds in plants due to elevation of stress caused by drought and other associated stresses is reported. Benefits of elevated secondary metabolites may be achieved in medicinal plants at the cost of sacrificing the biomass yield under stress condition [84]. Evaluation of photosynthetic activities and physiological state based on the time dependent changes of the chlorophyll a fluorescence has become the routine investigation in plant studies especially under stress environments. The application of chlorophyll a fluorescence imaging in plant research is growing rapidly, ranging from basic research at the cell and sub-cellular level to biotechnology or remote sensing of plant canopy and this technique has been developed as a versatile tool for determining and understanding the heterogeneity in a leaf photochemical efficiency [85]. The data on chlorophyll fluorescence parameters explaining damage via photo-inhibitory action had been used to differentiate between susceptible and tolerant genotypes of plants [86].

A severe and prolonged stress condition disrupts membrane integrity and causes permanent damage to PS II leading a decline in maximum (Fv/Fm) and thereby actual photosynthetic efficiency (F'v/F'm) in plants. It is accompanied with drastic decline in stomatal conductance in accordance to prevent water loss besides making a huge stomatal limitation to CO_2 influx which is one of the reason to reduced F'v/F'm. Hypothetically, in medicinal plants, a stress condition called optimum stress condition is one in which there is increase in secondary metabolites without significantly affecting the biological yield. However, a wide spectrum of group of secondary metabolites, different pheno-phases, preferred plant part for accumulation of secondary metabolites and life span makes it difficult to define an optimum stress condition. Further, soil type and climatic conditions of a region, continuous or simulated stress, duration of stress and coinciding phenophase makes the conditions very difficult in defining the optimum stress condition. A comprehensive response of different stress conditions at different growth stages on secondary metabolites content and growth in various plants is reviewed [87]. Recently, genotypic variation in andrographolide content is reported and their interaction with water deficit stress condition at different growth phase showed mixed response to andrographolide content in *A. panicuata* genotypes. In spite of increased per cent active ingredient content in some genotypes, a drastic decline in biological yield resulted in lower andrographolide yield in *A. panicuata* [88].

It is believed that a medicinal plant grown in semi-arid

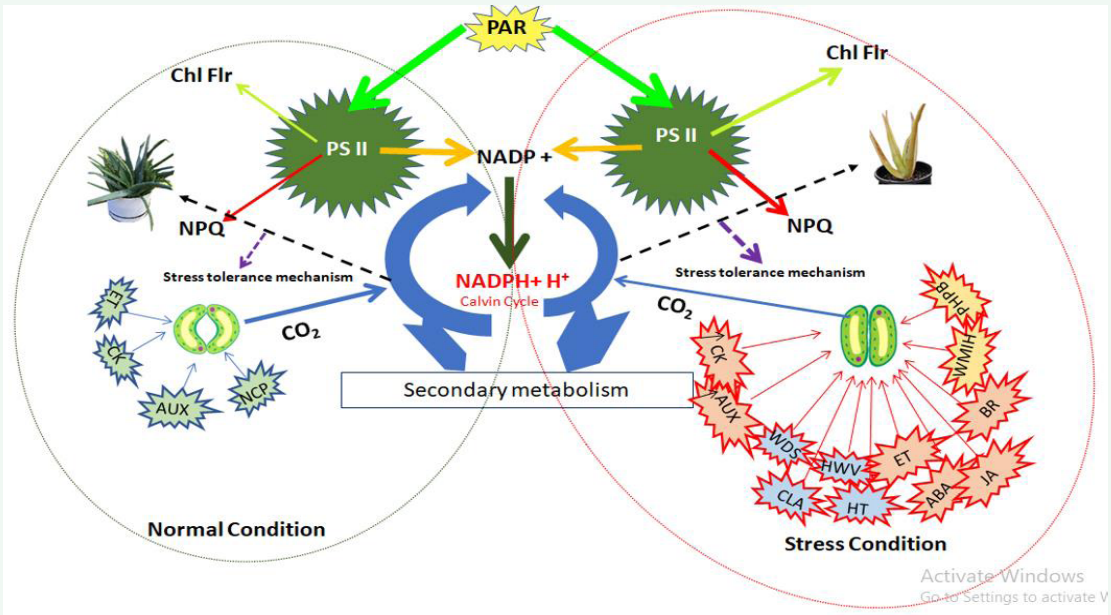

Figure 2 Absorbed energy distribution and utilization in plants under optimum and stress condition.
PAR Photosynthetically Active Radiation, Chl Flr Chlorophyll Fluorescence, NPQ Non-photochemical quenching, NADP Nicotinamide-adenine dinucleotide phosphate, ET* Ethylene, CK Cytokinins (Physiological concentrations), AUX Auxin (Physiological concentrations), NPC Other Normal physiological conditions (Absence of stress), WDS Water deficit stress, HT High temperature, CLA Constant light absorption, HWV High wind velocity, ABA Abscisic acid, JA Jasmonates, BR Brassinosteroids, CK↑ Cytokinins at high concentration, AUX↑ Auxin at high concentration, PHPB Exposure to plant and human pathogenic bacteria, WMIH Wounding; mechanical; insect; herbivores.

regions has elevated concentrations of active substances, i.e., secondary metabolites. Even stimulation of drought stress during the cultivation of medicinal plants is reported to impact product quality. Stomata have a great role to play in this case. Under normal conditions, the primary metabolism is the sink of electron flow. However, under stress conditions, the sink is shifted towards the secondary metabolism. Mahajan and his co-worker [89] has summarized effect of stress on secondary metabolites of some medicinal plants.

Explanation for stress-induced enhancement of natural products at anatomical level of stomata can be attributed to stress condition causing closing of stomata which reduces markedly the uptake of CO_2. Integration of environmental signals and endogenous hormonal stimuli regulates the opening and closing of stomata in plants. A complex network of signalling pathways controlling stomatal movements are activated in guard cells. Abscisic acid (ABA), a hormone of seqsuiterpene origin is a stress hormone causing closure of the stomata. Other phytohormones, like brassinosteroids and cytokinins also playing a role in stomatal development are involved in opening and closing mechanism in stomata. Jasmonic acid and ethylene are also involved in the stomatal response to stresses. ABA interacts with jasmonic acid and nitric oxide and this interaction results in stimulation of stomatal closure. A detailed phytohormone crosstalk on signalling pathways including the expression of specific genes and their impact on modulating stress response through the closing or opening of stomata has been reviewed by [81]. As a result of partial closure of stomata due to initial or mild stress conditions, a considerable decrease in the CO_2-fixation via Calvin cycle occurs. Resultantly, the reduction equivalents ($NADPH+H^+$) which were supposed to be utilized in primary metabolism is now made available, in a massive oversupply to secondary metabolic processes causing enhanced production of secondary metabolic processes. Some secondary metabolites as also reported to be useful in plant defence mechanism. Additionally genes of pathways leading to secondary metabolites are also up-regulated under stress condition [82] leading to synergistic effect in raised secondary metabolite production under adverse conditions [83]. However, under prolonged and severe stress conditions, stomatal movement imposes a huge limitations on gaseous exchange which in turn impacts both the primary and the secondary metabolism adversely, resulting in poor quality with significant biological yield loss. This is because during mild or initial stress condition, the photosystems are not permanently damaged and secondary metabolisms are the preferred sink for phosynthates as compared to the control conditions. Under severe stress conditions, the photosystems are permanently damaged causing reduced input of photo energy under the vicinity of scarcity of intracellular CO_2. Thus, stomatal movement has a great and crucial role to play especially in medicinal plants.

CONCLUSION

Stomata are the gate way of gaseous exchange between plant and the environment. Formation of stomata is under strict genetic control but is governed greatly by the conditions like temperature, light, pathogens etc. Alliance of the SPCH and the CRMS, through receiving signals from hormone and other signalling cascades, are vested with the responsibility of proper formation of stomata in plants. The association of FAMA, MYB88, FLP and RBR with the SPCH and the CRMS alliance is very much essential and

crucial in maintaining proper epidermal cell identity, asymmetric cell division, SD, spacing and or clustering. People normally recommend medicinal plants for lands otherwise unsuitable for field crops. Medicinal plants are different than conventional field crops in that in the former the quality of the produce depends on per cent content of secondary metabolites in general and principal active component in particular. In medicinal plants, secondary metabolites are increased during initial or mild stress condition at the cost of non-significant biological yield loss. Hypothetically, a stress condition which cause increase in secondary metabolites without significantly affecting the biological yield is called optimum stress condition. However, every plant has a different spectrum of group of secondary metabolites. They are also different in having different pheno-phase, life span, growth season, soil and climatic conditions and plant parts as specific target for secondary metabolite accumulation. Continuous or simulated stress, duration of stress and coinciding phenophase lead it to a further complex level. All this together make a very challenging condition in defining the optimum stress conditions that favours a quality produce without deviating the potential yield. Secondary metabolite yield; a product of the biological yield and the secondary metabolite content (%), is a base of economic yield in a medicinal plant. There is need to explore crop specific responses to stress imposed at different pheno-phases that may further help in exploring the optimum stress conditions.

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