

Floral induction pathways: Decision making and determination in plants to flower-A comprehensive review

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ARTICLE INFO

Article history:

Received on: December 07, 2020

Accepted on: December 31, 2020

Available online: March 10, 2021

Key words:

Photoperiodic pathway,

Autonomous pathway,

Gibberellin promotion pathway,

Vernalization pathway.

ABSTRACT

Reproductive success in angiosperms has remained dependent on the evolution of elaborate mechanisms that guarantee the flowering to occur at a favorable time. For the occurrence of floral transition at an opportune time, these regulatory mechanisms integrate varied environmental cues with the endogenous physiological ones. For understanding the underlying mechanisms of floral transition, genetic models have been developed based on the physiological studies carried on in the last century and the current molecular studies. Physiological experiments have been performed with diverse species, whereas studies mostly on *Arabidopsis thaliana*, a little flowering plant, have led to the development of current genetic models. This review will focus on the four-floral inductive pathways which operate in *Arabidopsis*: Photoperiodic, autonomous, gibberellin promotion, and vernalization pathways and how in this network of pathways, different nodes signify a site of signal integration and how the pathways are integrated, leading to a co-ordinated initiation of flowering.

1. INTRODUCTION

After discovering photoperiodic floral induction [1], many physiological studies have been carried on with the flowering transition. The physiological analysis and dissection of floral induction were made by introducing an experimental system based on the understanding that an external controllable stimulus can cause flowering when applied to a specific plant. The subsequent studies considered that higher plants share two essential features of floral transition: Generation of floral stimulus in leaves and its transport to the target, shoot apical meristem (SAM), which must be competent to receive it [2]. SAM's phase conversion to the reproductive stage is demonstrated by morphological changes accompanied by an alteration in gene expression [3]. The SAM occurs in two states, the incompetent state, unable to perceive signals of floral induction, and the competent state, capable of interpreting signals and leading to flowering transition. Thus, the SAM needs to pass the developmental checkpoint between incompetent and competent states. This transition leads to alteration in gene expression and organ production. Overcoming such checkpoints enables SAM to transform into floral meristem to produce flowers, and this transformation is induced by intrinsic and extrinsic stimuli that generate floral signals. Upon elimination of PNY (PENNYWISE) and PNF (POUNDFOOLISH) function in *Arabidopsis*, SAM remained in

a vegetative state as it could not perceive the inductive signals, which suggested the connection between meristem architecture and their response potential to floral stimuli [3]. microRNAs such as miR156 and miR172 and their corresponding targets are the key regulators of the phase changes in the floral transition [4].

2. FLORAL INDUCTION THROUGH SEVERAL PATHWAYS

Floral inductive signals induce the transformation of SAM into a floral meristem, and plants' flowering time could be affected by growing them in varying day lengths such as shortening day length by shading or increasing the day length by incandescent light bulbs [5]. Garner and Allard [1] put forward the concept of photoperiodism after examining a short day (SD) period requiring tobacco mutant. Other SD variety Maryland Mammoth was obtained from generally day-neutral (DN) tobacco (plants flowering at their own particular time irrespective of day length). In their night break studies (utilizing brief light exposure for interruption of extended night period), they established that duration of night controls SD plant's floral induction and not the day's length. Knott [6] demonstrated by restricting spinach leaves and SAM to lighting and shading that leaves are the organs where inductive signals originate. Chailakhyan [7] revealed that in *Perilla frutescens* and *Chrysanthemum*, grafting of induced leaves (donor) on recipient non-induced plants results in the recipient's early flowering. Hence, florigen theory was given by Chailakhyan, in which it was supposed that florigen formed in leaves represents a floral signal that when sent to SAM induces flowering. Both the quantity (length of light exposure) and the quality of light are essential signals for flowering, and plants

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possess specific receptors that perceive light exposure duration and differentiate between different wavelengths of light. Flowering is also affected by temperature, and certain wheat and rye varieties need to overwinter for flower induction. Gassner [8] showed that in winter variety flowering is accelerated if, during germination in pots, it is exposed to cold temperatures and subsequently transferred to the soil under normal temperatures. Lysenko [9] coined the vernalization term and found that increases in day length must follow cold temperature exposure. There are different developmental checkpoints that a plant must pass to flower. The intrinsic signals communicating growth status such as nutrient flow, hormones, and plant size, influence the floral induction. The studies evidence an endogenous floral inductive pathway's existence wherein a plant variety flowers only after producing leaves of a predictable number [10].

2.1. Photoperiodic Control of Floral Induction

The plants co-ordinate their flowering by utilizing a reliable indicator of environmental changes, "changes in day length," that can foretell the environmental changes like the cold period's arrival, allowing plants to adjust for flowering time. Flowering in SD plants occurs upon day length shortening, whereas, in long-day plants (LD), flowering occurs with the increase in day length, and in DN (day-neutral) plants flowering occurs irrespective of day length variations [2]. The plants are categorized further as obligate and facultative within the day length responses. Absolute inductive photoperiods are mandatory for obligate plants and such plants remain in a vegetative state without such requirement. In contrast, facultative plants show accelerated flowering under inductive conditions and undergo normal flowering even in noninductive photoperiod. It is now achievable to identify the loci and genes functioning in inductive day length determination by comparing the plant species and different varieties with dissimilar day length requirements for floral induction. Genomic loci functioning in flowering, or QTL (quantitative trait loci) in species such as rice and maize, are known and through dissection and QTL, rice flowering time genes have been identified and isolated [11]. OsCOL10, a CONSTANS-like gene, has been found to repress flowering by decreasing RFT1 and Hd3a (FT-like genes) expression through Ehd1. OsCOL10 works downstream of vital LD specific repressor, Ghd7, through the decrease of Ehd1 expression [12].

2.1.1. Photoreceptors: The light signal transducers

Phytochromes and cryptochromes, two essential types of photoreceptors in higher plants, play important role in flower induction. Phytochromes perceive far-red and red light, whereas cryptochromes perceive UVA and blue light. The day length response in *Arabidopsis* involves phytochrome A (PHYA) and B (PHYB) and cryptochrome 1 (CRY1) and 2 (CRY2) [13]. In *Arabidopsis*, blue light and far-red promote flowering, whereas red light confers inhibition. The photoreceptors interact with their corresponding interacting proteins within a complex network to transduce the light signals. Phytochromes and cryptochromes employ a mechanism that encompasses entrainment of the circadian rhythm to communicate the photoperiodic activity. The flowering time is also affected by additional inputs from temperature changes, light quality, and quantity through the endogenous clock [14]. An additional role is supposed for light in terms of its quality perceived by plants [15]. A critical component of a possible "light quality pathway" PFT1 (PHYTOCHROME AND FLOWERING TIME 1) gene in *Arabidopsis* [16], acts in disease resistance, suggesting of crosstalk between various environmental factors that affect plant development [17].

2.1.2. Self-reinforcing endogenous clock/the circadian clock

Plants use a predictable mechanism that utilizes day length variation for detecting seasonal changes. The endogenous clock compares light cycle and detects day length variations through its entrainment leading to periodicity setting. An endogenous mechanism called "circadian rhythm" can sense the light-dark cycle and result in self-reinforced gene expression in rhythmic patterns [18]. *Arabidopsis* clock design acts as a reference clock for other plants [19]. In plants responding to day length, the endogenous rhythm changes through the periodicity changes of the light/dark cycles lead to the flowering induction through the photoperiodic pathway. In a simple negative auto-regulatory feedback loop, translation of the clock gene and subsequent accumulation of protein in the nucleus inhibits its further transcription, and inhibition is relieved when both mRNA and proteins degrade, resulting in the renewal of the cycle. Three transcription factors (TFs) that interact to form such negative autoregulatory feedback loop in *Arabidopsis* are CCA1 (CIRCADIAN CLOCK ASSOCIATED1), TOC1 (TIMING OF CAB EXPRESSION1), and LHY (LATE ELONGATED HYPOCOTYL) [20,21]. CCA1 upregulates FERONIA (FER), a receptor kinase, which leads to alternative splicing and accumulation of some necessary flowering transition genes transcripts [22]. TOC1 inhibition by CCA1 and LHY, moreover, encompasses a co-repressor complex including, CONSTITUTIVE PHOTOMORPHOGENIC-10 (COP10), DEETIOLATED1, and DDB1 [23]. TOC1 is from a 5-member family of *ARABIDOPSIS* PSEUDO-RESPONSE REGULATORS (APRR) regulated through circadian rhythms. The circadian clock (CC) working alters downstream gene expression that coincides with favorable photoperiodic conditions for flowering. FAR-RED IMPAIRED RESPONSE1 (FAR1), FAR-RED ELONGATED HYPOCOTYL3 (FHY3), and HY5 activate ELF4 during the day, while ELF4 is repressed at dawn by CCA1 and LHY through direct interaction with these activators [24]. An increasing number of reciprocal interactions suggest an intricate web of connections operate the clock [25].

2.1.3. Photoperiodic induction integration through vital genes

In *Arabidopsis*, CONSTANS (CO) [Table 1], a critical gene encoding a zinc finger protein functioning as TF and controlling floral inductive pathway, is regulated through circadian rhythm [26]. CO regulates flowering positively in LDs and negatively in SDs [27]. Cloning of CO was done through a map-based approach [26]. The co-mutant flowers at a normal time in short days but late during long days, whereas overexpressing of CO imparts the plant's insensitivity to day length variation and results in early flowering [28]. The CC regulates CO expression on a 24-h cycle with its maximum at night. Hence, during short days, there is no overlapping of CO expression with the period of daylight, but in longer days, overlapping of CO expression and daylight in the evening occurs.

Light stabilizes CO expression, whereas during night CO protein is degraded through the proteasome, suggesting that the CC controls temporal CO expression. CDF (CYCLING DOF FACTOR) represses CO in the morning, whereas CDF2 and CDF1 are regulated through proteolytic degradation by a light-requiring complex of the clock proteins, GI (GIGANTEA), and FKF1 (FLAVIN-BINDING, KELCH REPEAT) [Table 1] [29]. FKF1 binds GI and targets CO's suppressors, resulting in CO expression [30]. GI's ability to bind CO promoter is restricted during the night as ELF4 regulates its entry to chromatin by sequestration into subnuclear bodies [31]. FKF1 activates CO and FT (FLOWERING LOCUS T) expression upon light activation and through COP1 homodimerization inhibition [Table 1] [32]. CRY2 and CRY1 inhibit COP1-SPA1 (COP1-SUPPRESSOR OF

PHYTOCHROME A-105) complex by sequestering SPA1 and result in CO protein stabilization [Table 1] [33]. Phytochrome A (phyA) disrupts COP1-SPA1 complex upon far-red activation in the afternoon, while in the morning, phytochrome B (phyB) mediates the CO protein degradation [34]. PSEUDO-RESPONSE REGULATORS (PRR 1, 5, 7, and 9) stabilize the CO product in the late afternoon through repression of CDF1 [35]. Another floral repressor, COL4 (CONSTANS LIKE 4), co-localizing with CO in the nucleus, acts antagonistically to CO and provides another floral regulation level [36] [Figure 1].

Two regions, a zinc-finger motif and a CCT region of CO protein, are vital for its proper functioning. CCT region found in TOC1, CO, and CO-LIKE genes help in the nuclear localization of these proteins [37]. FKBP12 in *Arabidopsis* interacts with CCT domain of CO affecting its stability and hence function [38]. Although expressed in several cell types, CO expression specific to companion cells confers timely flowering, and that if expressed only in SAM, early flowering does not occur [39]. Confinement of CO expression to small veins' companion

cells using galactinol synthase promoter results in timely flowering under noninductive SDs. Flowering was also accelerated in co-mutant receptor plants when the leaves expressing minor vein CO were grafted to them [40]. Thus, CO is supposed to mediate the floral stimulus generated through photoperiod in leaves and transporting it to SAM by the phloem. CO and FT expression is promoted by PFT1/MED25 (a subunit of mediator complex, which bridges RNA polymerase II and transcriptional factors) in a CO-independent manner [41]. The function of PFT1 is governed by photoperiod and length of short tandem repeat region that encodes 90 amino acid regions rich in glutamine [42].

FT protein is a direct downstream target of CO, and genetic screen of CO overexpressing lines led to the isolation of *ft* mutants that flower late. As FT represses the overexpression phenotype, its position can be suggested as down-stream of CO and specifies that an alternative target gene exists, acting parallel to CO. In LDs, the CO protein peaks in the late afternoon bind to the FT promoter and interact with the NF-Y–FE complex resulting in FT transcriptional activation [43].

Table 1: Candidate genes play their roles in different pathways of floral induction.

Pathway of floral induction	Candidate genes
Photoperiodic pathway	CONSTANS (CO) [26], GIGANTEA (GI), FLAVIN-BINDING, KELCH REPEAT (FKF1) [29], CONSTANS LIKE 4 (COL4) [36], PSEUDO RESPONSE REGULATORS (PRR1, 5, 7, and 9) [35], CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1) [32], CRYPTOCHROME CIRCADIAN REGULATOR 1 & 2 (CRY1 & CRY2) [33], PHYTOCHROME A (PHYA) [34], FLOWERING LOCUS T (FT) [32], PICKLE (PKL) [45], HOMOLOG OF TRITHORAX1 (ATX1) [45], FT-INTERACTIVE PROTEIN 1 (FTIP1) [47], SYNTAXIN OF PLANTS 121 (SYP121) [47], QUIRKY (QKY) [47], SODIUM POTASSIUM ROOT DEFECTIVE 1 (NaKR1) [43], FLOWERING LOCUS D (FLD) [59], TERMINAL FLOWER 1 (TFL1) [49], Transcriptional factors TCP17, TCP13, TCP5, SQUAMOSA PROMOTER-BINDING-LIKE PROTEIN 3 (SPL3), SPL4, and SPL5 [50], APETALA 1 (AP1) [129].
Autonomous pathway	FLOWERING LOCUS C (FLC) [60], LUMINIDEPENDENS (LD), SUF4 (SUPPRESSOR OF FRIGIDA) [61], FLOWERING LOCUS CA (FCA) [55], FLOWERING LOCUS Y (FY) [55], FLOWERING LOCUS D (FLD) [59], PCF11P-SIMILAR PROTEIN 4 (PCSS4) [60], FLOWERING LOCUS VE (FVE), HISTONE DEACETYLASE 5 (HDA5), HISTONE DEACETYLASE 6 (HDA6), RELATIVE OF EARLY FLOWERING 6 (REF6), EARLY IN SHORT DAYS 4 (ESD4), and DBP1 (DNA-BINDING PROTEIN PHOSPHATASE 1) [61, 62].
Vernalization pathway	FLOWERING LOCUS C (FLC) [60], VERNALIZATION 1 and 2 (VRN1 and 2) [77], VERNALIZATION INSENSITIVE 3 (VIN3) [69], VERNALIZATION 5 (VRN5) [79], LIKE HETERO-CHROMATIN PROTEIN 1 (LHP1), VP1/ABI3-LIKE 1 (VAL1) and VAL2 [79,80].
Gibberellin promotion pathway	AtMYB33 [88], Repressor of <i>ga1-3</i> (RGA), GIBBERELLIC ACID INSENSITIVE (GAI) [90], JASMONATE-ZIM (JAZ1) [96], GA3-oxidase2 (GA3ox2), GA30x1 [102], TEM1 (TEMPRANILLO 1) and TEM2, SHORT VEGETATIVE PHASE (SVP) [103].

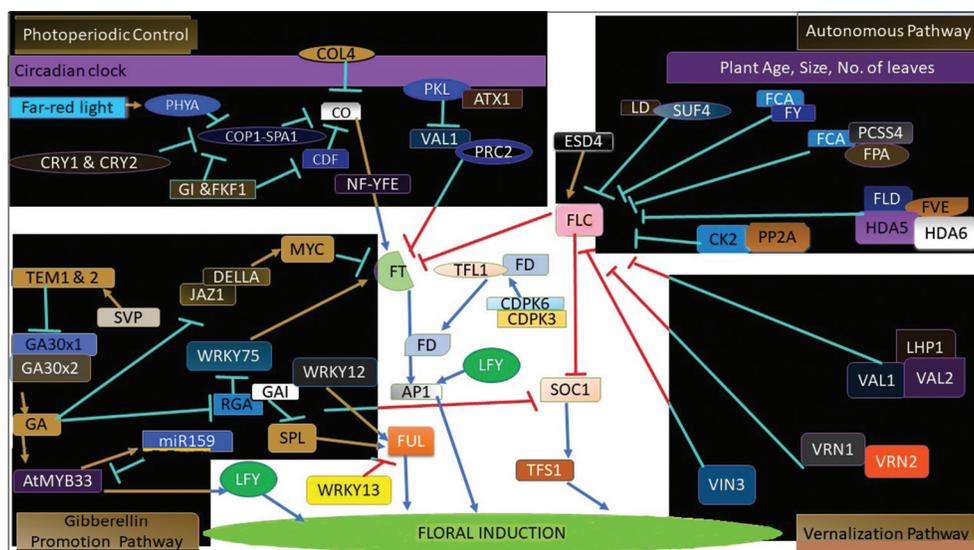


Figure 1: Mechanisms of floral induction and integration of different pathways.

VAL1 (VIVIPAROUS1/ABSCISIC ACID INSENSITIVE3-LIKE1) binds to FT and arranges polycomb repressive complex 2 (PRC 2) components to silence the FT epigenetically at night and before dusk [44]. The PRC2 silencing of FT is prevented by the interaction of PICKLE (PKL) with CO and ATX1 (HOMOLOG OF TRITHORAX1) [Table 1] [45]. Multiple enhancers affecting the flowering time seem to regulate FT in inductive conditions, and one such enhancer was identified recently [46]. FT-INTERACTIVE PROTEIN 1 (FTIP1), ER membrane protein, facilitates export of FT to sieve elements and FT movement through companion cell plasmalemma is regulated by the interaction of SYP121 (SYNTAXIN OF PLANTS 121) with QKY/MCTP15 (QUIRKY) [Table 1] [47]. From leaves, FT transport to SAM is facilitated by NaKR1 (SODIUM POTASSIUM ROOT DEFECTIVE 1) after its activation through interaction with FE and CO [43]. At SAM, FT complexes with FD (B-zip TF), regulating the expression of downstream targets like AP1 (APETALA 1) [48]. TFL1 (TERMINAL FLOWER 1), a floral repressor, remains bound to FD in an elaborate (FD-TFL1 complex), maintaining the FD in an inactive state at SAM, and activation of FD into a florigen activation complex (FAC) occurs through its phosphorylation catalyzed by CDPK6 (CALCIUM DEPENDENT PROTEIN KINASE 6) and CDPK33 [49] [Figure 1]. TFs, TCP17, TCP13, TCP5, SPL3, SPL4, and SPL5 interact with FD and facilitate its DNA binding and activating AP1 expression [Table 1] [50].

The homologs for CO and FT occur in both dicot and monocot species, suggesting their role in flower transition in other plants. The CO complemented the loss of co-function in *Arabidopsis* mutants from *Pharbitis nil* and *Brassica napus* [51]. The QTL related to flowering time mutants in rice, called *Heading date*, encodes CO and FT genes. *Heading Date 1 (Hd1)*, CO homolog, affects the early transition and inhibition of flowering in inductive SD conditions and LD conditions, respectively. *Hd1* displays a diurnal expression pattern with highest levels at night and dawn under LD conditions, coinciding with the CC expression pattern [52]. The *hd1* mutants, exhibiting late-flowering phenotype, show lower expression levels of an essential flower timing gene *Heading date 3a (Hd3a)*, which share high sequence to FT gene [53], and *hd3a* mutants show late flowering under SD conditions than wild-type plants. Thus, in rice, the CO/FT interaction seems to be preserved, though SD, not the LD, induces flowering in rice. *Hd1* inhibits *Hd3a* expression under LD and induces it under SD when the *Hd3a* expression reaches highest during the day and with no expression under LD treatments [52]. As the CC regulates the family of CO-like genes in both dicots and monocots, the photoperiodic inductive mechanism can be said to be evolutionarily conserved. Even though CO and FT are conserved in numerous species, other self-determining parallel mechanisms regulate photoperiodic floral induction.

3. AUTONOMOUS PATHWAY

Most plants' flowering occurs without extrinsic inductive signals and plants that exhibit obligate requirements of such extrinsic signals are infrequent. Thus, additional intrinsic factors are supposed to provide signals for floral induction. Such constitutive or autonomous signals are derivative of the plant's physiological outputs that determine the readiness to flower such as plant age, size, or the number of leaves. These endogenous signals are possibly related directly to the number of plant accumulated resources [54]. Several mutants in *Arabidopsis* flower late irrespective of noninductive and inductive photoperiods and represent the autonomous pathway, different from the photoperiodic pathway. However, many such mutant genes react to the vernalization pathway elements, suggesting the intersection of these two pathways at

specific points. The general assumption about the autonomous signal is that it consists of nutrient combinations and phytohormones such as cytokinins or gibberellins, which move to SAM from leaves to induce flowering [54]. Other factors that can be part of the signal might be RNA and proteins in phloem sap. However, the precise nature of these components is yet to be revealed. Nevertheless, genes involved in the autonomous pathway encode factors that maintain the epigenetic state and RNA processing of critical genes [55]. FLOWER ING LOCUS C (FLC) gene in *Arabidopsis* is a shared component of vernalization and autonomous pathways that act as an essential node for signal integration and offers a valuable model to understand floral inductive signals' molecular nature [Table 1].

3.1. Flowering Locus C (FLC) Integrate Various Floral Inductive Pathways

The autonomous pathway involved genes were recognized in *Arabidopsis* as mutant plants flowering late in LD or SD conditions, unrelated to day length [56]. The first such gene isolated is LUMINIDEPENDENS (LD), which specifies a homeodomain protein suppresses FLC expression through interaction with SUF4 (SUPPRESSOR OF FRIGIDA) and epigenetically through histone modification [Table 1] [57]. FLC, encoding MADS-box protein, suppresses many genes involved in floral induction such as FT and SOC1 and is positively and negatively regulated through control of transcription by many regulators in a dosage-dependent pattern [58]. FCA (FLOWERING LOCUS CA) and FLY (FLOWERING LOCUS Y) are the two other genes that function in the autonomous pathway, and interaction between these represses the FLC expression [Table 1] [55]. FCA has an RNA-binding domain that is supposed to interact directly with FY. The FCA-FY complex causes early polyadenylation of the FLC transcript during intron splicing, resulting in the FLC transcript's untimely termination. FLD (FLOWERING LOCUS D) interaction with FCA and FPA (FLOWERING LOCUS PA) links the RNA processing to regulation at the chromatin level, and this interaction is at least partially necessary for the floral transition [59]. PCSS4 (PCF11P-SIMILAR PROTEIN 4) also interacts with FCA to regulate alternate RNA processing [60] [Figure 1].

The autonomous pathway also induces flowering by regulating genes through epigenetic control. Repression of FLC expression is done by FLD, FVE (FLOWERING LOCUS VE), HDA5 (HISTONE DEACETYLASE 5), HDA6 (HISTONE DEACETYLASE 6), LD (LUMINIDEPENDENS), and REF6 (RELATIVE OF EARLY FLOWERING 6) genes through transcriptional silencing [Table 1] [61,62]. FLD and FVE are involved in histone deacetylation of the FLC locus, presumably modifying the FLC transcript level in the process [63]. Interaction of HDA5 with HDA6 and FLD and FVE suggests co-repressor complex formation providing a relationship between histone demethylation and deacetylation for FLC regulation [61,62]. FLC is repressed by CK2 (casein kinase 2) and PP2A (protein phosphatase 2A) through modifications of phosphorylation and dephosphorylation, respectively, at the posttranslational level [64]. ESD4 (EARLY IN SHORT DAYS 4) mediated sumoylation positively regulates the FLC mediated floral repression [65] [Figure 1]. DBP1 (DNA-binding protein phosphatase 1) acts in autonomous and photoperiod pathways of flowering by modifying transcript levels of many critical integrators such as CO, LFY, SOC1, FLC, and FT [66]. Dehydroabietinal mediates upregulation of the autonomous pathway involved genes such as FLD, FVE, and REF6 resulting in FLC repression [67]. Furthermore, two KH domain proteins KHZ1 and KHZ2 are supposed to act as heterodimers, leading to the repression

of FLC pre-mRNA splicing efficiency [68]. Thus, FLC functions as a floral induction node in *Arabidopsis* as multiple mechanisms act in FLC levels' autonomous regulation.

4. VERNALIZATION PATHWAY

Exposure to temperature, especially low temperature (vernalization), helps regulate the plants' onset of flowering. Vernalization thus is regarded as a checkpoint mandatory to be crossed by several plants to undergo flowering [69]. The SAM perceives the signal of vernalization and floral induction in several plants depends on the subsequent photoperiodic response after their prolonged exposure to cold temperature, avoiding precocious flowering because of a short warm spell before the arrival of cold conditions. Vernalization includes two separate processes, perception of a prolonged spell of cold temperature and "remembering" that perception to induce flowering later in the spring or summer. The vernalization represents the somatically heritable condition, induced by prolonged cold exposure that the descendant cells retain from vernalization-induced SAM cells [70].

4.1. FLC Repression Mediates Vernalization in *Arabidopsis*

Prolonged exposure to cold decreases the FLC transcript level quantitatively in plants, and this decreased FLC expression is preserved even after the plants are transferred to warmer environments [71]. Based on the maintenance of a repressed FLC state, temporal partitioning between the cold treatment timing and the onset of the flowering, it is hypothesized that the vernalization functions through epigenetic control of FLC repression.

The vernalization or extended cold periods in *Arabidopsis* encompasses several steps that ultimately cause FLC's stable repression, and this state is mitotically heritable [72]. Non-vernalized plants exhibit active conformation of FLC chromatin, that is, highly modified chromatin, such as acetylation of H3K9 and H3K14 (lys 9 and 14 of histone 3) and methylation of H3K4 (lys 4 of histone 3), which represent trademarks of active genes [73]. Levels of such active modifications get reduced by vernalization, and histone 3 of FLC chromatin becomes highly methylated at lys 9 (H3K9) and 27 (H3K27) [74], leading to FLC repression and mitotic inheritance of FLC silenced state through action and autoregulatory loop establishment of repressor complexes on these sites. The epigenetic state is reset in every generation, ensuring vernalization requirement remains for each plant generation [75]. At the FLC locus, histones are hypo-acetylated by VIN3, a plant homeodomain (PHD) protein, resulting in chromatin remodeling through protein-protein interactions [69]. Restriction of VIN3 expression to cold periods evidences its action in the primary FLC inactivation but not in the suppression following exclusion from cold environments [76]. FLC repression stabilizes by the action of two other genes, VERNALIZATION 1 and 2 (VRN1 and 2) that maintain the repressed FLC state and propagate the "memory" of cold exposure because mutants, *vrn1* and 2, cannot maintain vernalization-induced repressed FLC state with the return of warm temperatures [Table 1] [77]. VRN1 specifies a nuclear-localized DNA binding protein, binding DNA in a non-sequence specific means [77], and acts through the vernalization dependent and independent pathway, as evidenced by overexpression analysis. Non-vernalized overexpression lines show an enhanced floral transition without any variations in FLC levels. Overexpression of VRN1 activates FT that initiates the floral transition [77]. VRN2 specifies a zinc-finger protein, a polycomb group protein that acts in the stable repression of

genes but not in the repressed state's initiation [78]. Polycomb gene products in *Arabidopsis* interact and form multimeric complexes functioning as a histone methyltransferase. A complex called Polycomb Repression Complex 2 (PRC2)-like complex, identified in *Arabidopsis*, contains VRN2, CURLY LEAF (an enhance of Zeste homolog), SWINGER (an E (z) homolog), and FERTILIZATION-INDEPENDENT ENDOSPERM. This complex is also said to interact with VIN3 and VRN5 (VERNALIZATION 5) to function in the early phases of vernalization facilitated FLC repression [76]. LHP1 (LIKE HETERO-CHROMATIN PROTEIN 1) helps in maintaining the repressed FLC state after cold exposure through its interaction with VAL1 (VP1/ABI3-LIKE 1) and VAL2 [79,80] [Figure 1]. Although LHP1 does not help in histone methylation, methylation of H3K9 and H3K27 may enhance the ability of LHP1 to maintain an FLC silenced state. Thus, a complex formation by these proteins is suggested that facilitate the proliferation of the repressed state of genes through cell divisions. FLC's rapid repression occurs through the interaction of VAL1 and VAL2 with HDAC9 and PRC2 that mediate deacetylation and later trimethylation of H3K27 [81].

5. GIBBERELLIN PROMOTION PATHWAY

In *Arabidopsis*, gibberellic acid (GA) affects the flowering time is well known. The GA application results in premature flowering in LD and SD and bypasses several mutants' late-flowering phenotype from the rest three pathways [82]. Environmental and developmental signals regulate the GA's biosynthesis and signal transduction; besides, GA, turnover, and concentration are most important [83]. GA promotes flowering through FT activation in leaves, and *gal-3* (GA-deficient) mutant plants show reduced FT expression while exogenous GA application to such plants increases the FT expression [84,85].

The signal generation by GA1, GA pathway's early step, produces copalyl pyrophosphate from geranylgeranyl pyrophosphate, but the signal that induces GA1 is unknown. GA's role in floral induction is established by the GA biosynthesis deficient mutants, which cannot flower in SDs because of active GA absence [86]. Mutational scrutiny of genes involved in the GA pathway shows that it is not the GA itself but the generation of the signal that leads to floral induction. The molecular targets for GA first defined in barley defined GAMYB gene as critical for GA signal transduction. The effects of GA application get mimicked by over-expression of GAMYB [87]. GAMYB binds to GARE (GA-response element), distinct DNA sequences within promoters of genes upregulated by GA. Three genes in *Arabidopsis* exhibiting similarity to barley GAMYB have been found, and among these, AtMYB33 shows the highest resemblance. AtMYB33 acts in *Arabidopsis* flowering through binding to the GARE sequence upstream of LEAFY [Table 1]. For regulating floral induction, AtMYB33 is presumed to act along with additional LFY inducers like SOC1 [88] [Figure 1].

Two floral transition repressors, RGA (Repressor of *gal-3*) and GIBBERELLIC ACID INSENSITIVE (GAI), both of which are DELLA class proteins, are affected by GA [89]. DELLA proteins possess a DELLA domain at N-terminal, which is presumed to act as the target for GA-directed ubiquitination subsequently proteasome-facilitated destruction. The finding evidences the importance of RGA and GAI in inhibiting the flowering that GAI represses SOC1 expression, but no such direct effect of GAI on LFY is found [90]. GAI and RGA suppress the microRNA miR159, a 21-bp sequence with substantial identity to the AtMYB genes [91]. miR159 overexpression leads to decreased AtMYB33 levels in leaves resulting in a significant

delay in flowering. The lower AtMYB33 levels are possibly due to miRNA-facilitated destruction. miR159 levels seem to vary with variations in the GA signaling pathway and in response to auxin and ethylene that affect DELLA protein levels [90]. AtMYB33, having a putative GARE motif, regulates miR159 positively, proposing overexpression prevention through a negative feedback loop resulting in early flowering. SOC1 repression in *Arabidopsis* is supposed to be overcome by GA-facilitated DELLA proteins ubiquitination, and proteasome-mediated protein degradation [90]. Floral repression is alleviated, and LFY expression is induced by promoting SOC1 and AtMYB33 when the GAI and RGA are degraded. DELLA proteins interact with CO, disrupting its function, and preventing it from binding FT promoter and downregulate it [92]. DELLA proteins can also suppress flowering by inhibiting CO to interact with NF-Y and interact with PIF4 preventing its binding to the FT promoter [93]. DELLA proteins show interaction with FT suppressors such as MYC3, a bHLH TF, and suppressing FT expression. Under SD conditions, lower GA levels promote a higher level of DELLAs and MYC3, showing enhanced expression, stabilized by DELLAs out-compete CO, thereby repressing FT expression and eventually prevent precocious flowering [94]. DELLAs can interact with FLC, promoting downstream genes, including FT [95]. FT expression is also mediated in both SDs and LDs through MYC function modulation by DELLAs, involving JA signaling. The competition between MYC2 and DELLAs to bind JAZ1 (JASMONATE-ZIM) protein determines the JA-mediated gene expression [Table 1] [96]. DELLAs bind to JAZ1 and free MYC at low GA levels promoting JA-mediated gene expression, whereas DELLAs get degraded at high GA levels, and the MYC2-JAZ1 complex formed represses the JA-mediated genes. As JA represses the flowering, such repression occurs through MYC2 binding directly to FT promoter in LDs and pointing toward the existence of DELLA-MYC2-JAZ1 module for floral induction [97] [Figure 1].

DELLA proteins antagonize a universal GA response promoter, PKL, and compromise the SPL gene activation at the transcriptional level, whereas post-translationally, DELLA proteins inhibit SPL transactivation activity through binding them [98,99]. Furthermore, DELLAs and SPLs function antagonistically on common gene targets such as FUL and SOC1 [99]. WRKY TFs, containing WRKY domains of 60–70 amino acids, also are involved in GA mediated floral induction such as WRKY 12 and 13 interact with RGL1 and GAI modulating the transcriptional activity of WRKYs [100]. In SDs, WRKY 12 and 13, though both are expressed in SAM, WRK12 promotes FUL expression while WRK13 represses it, thereby exhibiting the opposite role in floral regulation [Figure 1]. Likewise, WRKY75 is also inhibited by its interaction with DELLAs such as GAI, RGA, and RGL1, thereby not allowing FT expression [101].

GA biosynthesis regulated spatially and temporally also mediates the floral induction. GA biosynthesis genes show spatial regulation, as is evidenced by the leaf vasculature localized accumulation of GA3ox2 (GA3-oxidase2), which catalyzes GA precursor conversion into bioactive GAs [102]. TEM1 (TEMPRANILLO 1) and TEM2, TFs that repress FT, suppress GA3ox2 and GA3ox1, contributing to the diurnal GA3ox1 expression pattern in SDs [103]. The increased level of GA20ox2 (GA20-oxidase2) in the SAM under LD conditions is partly attributed to the downregulation of SVP (SHORT VEGETATIVE PHASE), floral repressor [104]. Along with FLC, SVP also regulates other GA metabolic genes like GA2ox8, and SVP/FLC complex regulates GA3ox1 indirectly by promoting TEM2 and suppression of TEM1 [105] [Figure 1]. The conserved regulatory pathway functions for different developmental purposes as microRNA regulation,

and the GA-facilitated DELLA protein destruction and pathway of DELLA protein repression have been found in other plants and other developmental pathways.

6. MEANS OF FLORAL TRANSITION INTEGRATION AND INSTIGATION

Notwithstanding the signal's origin, floral induction's ultimate purpose is SAM's transformation to the reproductive state [106]. There occurs convergence of pathways of flowering time in particular genes called flowering-time integrators. In *Arabidopsis*, many floral pathways that perceive different developmental and environmental stimuli converge to some integrators of flowering such as FT, AGL24 (AGAMOUS-LIKE 24), and SOC1 (SUPPRESSOR OF OVEREXPRESSION OF CONSTANS 1) [107] that are activated through downregulation of FLC as in the autonomous and vernalization pathways, through CO-regulated CONSTANS (CO) expression as in photoperiodic pathway or directly as in gibberellin promotion pathway. PhyB interacting proteins, VASCULAR ONE ZINC FINGER 1 and 2 (VOZ1 and 2), function in the photoperiodic and vernalization pathways, as double mutants voz1 voz2 flower late and show increased FLC expression without vernalization, whereas vernalization exposure reverses such phenotype [108].

ICE1 (INDUCER OF CBF EXPRESSION 1) integrates the vernalization and photoperiod pathways through SOC1 and FLC regulation. Under cold temperature, ICE1 binds FLC promoter and leads to delayed flowering, whereas inductive LDs lead to SOC1 activation, which prevents FLC activation through ICE1 [109]. LFY positively regulates AP1, and flower commitment is determined through AP1-LFY positive feedback interaction [Figure 1]. Thus, all pathways intersect at the activity of a subset of flowering-time integrator genes, either directly or through FLC. At a given time, flowering-time genes face some degree of inhibition due to FLC activity and some degree of activation due to CO activity and gibberellin-induced signals. Flowering-time integrators will express, and the floral transition will occur only when activation signals are more robust than FLC-based inhibition.

6.1. Role of Flowering-time Integrators

The flowering-time regulators act either directly or indirectly as transcriptional regulators and activate a subset of genes called floral meristem identity genes (FMI) that operate at the SAM to make it determined to produce flowers. The activity of each of the flowering-time integrators depends on FMI gene expression. Not only is the regulatory activity of each flowering-time integrator slightly different but also the output pathways that lead to them vary slightly as well [110].

6.1.1. Flowering locus T

Koornneef, *et al.* [111] identified one of the original late-flowering lines, the *ft* mutant, which showed normal LEAFY (LFY) expression, but *lfy* and *ft* double mutant exhibited significantly reduced expression of the FMI gene, AP1. FT functions in signal transduction and its expression occur mainly in the leaf and are then transported to SAM, inducing the floral transition through FD interaction. Several TFs regulate FT expression in response to different stimuli. CIB1 (CRYPTOCHROME-INTERACTING BASIC-HELIX-LOOP-HELIX1), CO, MRG2 (Morf-related Gene 2), WRKY71, and PIF4 (PHYTOCHROME-INTERACTING FACTOR 4) directly activate the transcription of FT [112,113]. Direct repression of FT is carried by TEM 1 and 2 (TEMPRANILLO), SVP (SHORT VEGETATIVE PHASE), TOE 1 and 2 (TARGET OF EAT), EFM (EARLY-

FLOWERING MYB PROTEIN), CDF1 (CYCLING DOF FACTOR1), SNZ (SCHNARCHZAPPEN), and SMZ (SCHLAFMUTZE) [Table 1] [114,115]. Hence, FT acts as an essential member in controlling the flowering time in *Arabidopsis*. The photoperiodic induction pathway induces FT expression, while FLC represses its expression. The vernalization and autonomous pathway induce FLC expression indirectly, while in the gibberellin promotion pathway, DELLA proteins downregulate FT expression. Kobayashi *et al.* [112] provided the first evidence of FT induction by photoperiodic pathway. This group of researchers fused a glucocorticoid receptor from rat to CO and ectopically expressed the construct in *Arabidopsis*. The expression of FT showed rapid induction when the treatment of steroids induced CO activity. Daylight FT expression induction by CO suggests photoperiodic control to the system [116]. FT receives the inhibitory signals from FLC simultaneously, and FT transcripts are not found in transgenic plants expressing FLC ectopically [117]. FT transcription inhibition occurs when the FLC protein binds to FLC's first intron as a multi-protein complex [118]. The FT protein induces flowering when it is transferred from induced leaves to shoot apical meristem.

6.1.2. Suppression of overexpression of *constans1* (SOC1)

SOC1 (MADS-box TF) upregulates another direct target of CO as in SOC mutants early floral phenotype in CO overexpressing lines is suppressed and exhibiting delayed flowering similar to ft mutants. However, in double mutant *ft soc1* with CO overexpression, flowering delays same to those of *co* mutants. Thus, SOC1 and FT seem the two vital downstream CO targets, which act in parallel, partly redundant induction pathways. FT and SOC1 upregulate AP1 (APETALA1) and LFY (LEAFY), two FMI genes. SOC1 helps integrate signals from several pathways and transmit the integration to LFY [119]. Vernalization and day-length pathways regulate the SOC1 expression [117]. CO upregulates the SOC1 expression in LDs through the FT protein, and SOC1 integrates GA-induced signals for flowering with environmental cues [120]. Although SOC1 being the primary player, AGL72, AGL71, and AGL42 function in GA-mediated floral transition [121]. SOC1 and FLC affect flowering oppositely, bolting inducing gene TFS1 (TARGET OF FLC AND SPV1) is repressed by FLC through chromatin modulation while SOC1 upregulates it through histone demethylase recruitment, REF6 (RELATIVE OF EARLY FLOWERING 6), and enzyme BRAHMA [122]. FLC binding directly to the SOC1 promoter or interacting with SVP, which then binds SOC1, results in SOC1 repression [123]. AGL24 counteracts these floral repressors, dimerizes with SOC1, and acts through a positive feedback loop to induce SOC1 [124]. SOC1 expression is regulated transcriptionally by miRNA156 and SQUAMOSA BINDING FACTOR LIKE9, post-transcriptionally by ELF9 (EARLY FLOWERING 9), and post-translationally by a PIN1 type parvulin and epigenetically by SHL, ensuring threshold level of SOC1 to trigger floral transition at the appropriate time [125]. SOC1 upregulates the LFY by binding its regulatory sequences, which results in the activation of AP1, subsequently, the floral initiation [123].

6.1.3. LEAFY and APETALA1

The severe *lfy* and *ap1* mutants of *Arabidopsis* show a phenotype where floral organs get replaced by vegetative characteristics [126]. All higher plants have a unique transcriptional factor, LFY, which directly targets FMI genes such as AP1 and CAULIFLOWER [41]. LFY plays a vital role in integrating floral inductive signals from diverse pathways and initiation of FMI genes. LFY is a regulator of AP1, and a positive feedback interaction of LFY and AP1 determines the assurance to flower. The binding site of LFY at the AP1 locus is essential for locus

expression, and the interaction between the AP1 locus and LFY is now structurally characterized [127]. Linker histone (H1) is displaced, and chromatin remodelers, SWI/SNF, are recruited by LFY at AP1 locus to induce AP1 expression, though higher locus opening associated with higher AP1 expression occurs at a later stage [128]. The transcription of AP1 causes activation and regulation of specific FMI gene expression, assuring the floral transition [129]. Gibberellins impact the floral transition by regulating SOC1, and from multiple pathways, signals are integrated, and SOC1 conveys the result to LFY [119].

7. CONCLUSION AND FUTURE PERSPECTIVES

Much research has been done to know the underlying mechanism of floral induction in different flowering plants. First, the focus was laid on the physiological experiments to understand the significant cues which lead to the floral induction, and then attention was shifted to the molecular approaches to know the key genetic players involved and their possible role in this process. External stimuli are essential for the plants to undergo flowering, but in most plants, flowering can occur in the absence of such stimuli, suggesting intrinsic factors to plant growth provide the floral induction signals. Multiple complex pathways regulate floral induction. Many key genetic players have been discovered to be either specific to a floral induction pathway or are playing their role in other floral induction pathways, suggesting the possible intersection of different floral induction pathways. The regulation of these pathways occurs at the genetic as well as the protein level. microRNAs (microRNAs) regulate the specific genes acting in floral induction both at transcriptional and post-transcriptional levels. The pathways mediating floral induction has several nodes that signify the site of signal transduction, and the pathways are integrated that result in a co-ordinated initiation of flowering. Despite much research going on, the full mechanism operative in floral induction is not yet apparent. Not much is known about how the known floral regulators integrate into the flowering gene network and their target genes and activity mechanisms. Furthermore, how the collective action of TFs, epigenetic regulators, hormones, and small RNAs controls the floral induction needs to be fully unraveled. Future research can target such aspects by employing novel molecular approaches such as proteomics, genomics, transcriptomics, and targeted genome engineering approaches like CRISPR/CAS system to establish and perfect floral induction molecular mechanisms.

8. AUTHORS' CONTRIBUTIONS

Authors Latif Ahmad Peer, Mohd Yaqub Bhat, and Bilal Ahmad Mir contributed to the conception of the study, preparation and design of this review article. The literature survey was done by the author Latif Ahmad Peer. Latif Ahmad Peer wrote the first draft of the manuscript and all authors made their comments on it. All authors read, revised, and approved the final manuscript.

9. CONFLICTS OF INTEREST

The authors declare no conflict of interest

10. FUNDING

There is no funding to report.

11. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

12. PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

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How to cite this article:

Peer LA, Bhat MY, Ahmad N, Mir BA. Floral induction pathways: decision making and determination in plants to flower-A comprehensive review. *J App Biol Biotech.* 2021;9(2):7-17. DOI: 10.7324/JABB.2021.9201