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Transcription Factors and MicroRNA Interplay: A New Strategy for Crop Improvement

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Abstract

MicroRNAs (miRNAs) and transcription factors are master regulators of the cellular system. Plant genomes contain thousands of protein-coding and non-coding RNA genes; which are differentially expressed in different tissues at different times during growth and development. Complex regulatory networks that are controlled by transcription factors and microRNAs, which coordinate gene expression. Transcription factors, the key regulators of plant growth and development, are the targets of the miRNAs families. The combinatorial regulation of transcription factors and miRNAs guides the appropriate implementation of biological events and developmental processes. The resources on the regulatory cascades of transcription factors and miRNAs are available in the context of human diseases, but these resources are meager in case of plant diseases. On the other hand, it is also important to understand the cellular and physiological events needed to operate the miRNAs networks. The relationship between transcription factors and miRNA in different plant species described in this chapter will be of great interest to plant scientists, providing better insights into the mechanism of action and interactions among transcription factors (TFs) and miRNA networks culminating in improving key agronomic traits for crop improvement to meet the future global food demands.

Keywords: transcription factors, microRNA, regulatory network, interplay, gene expression

1. Introduction

In the recent years, various regulatory complex networks have been identified in plants [1]. Identification of these networks has led to better understanding gene regulation at

transcriptional and post-transcriptional level. In this chapter, we will be emphasizing on interplay of TFs and miRNAs as a major regulatory mechanism during and after mRNA synthesis. TFs interact with enhancers at transcriptional level to regulate gene expression and have been well recognized in the last decade [2]. This is also supported by the discovery of diverse family of TFs playing various roles in plants [3]. Post-transcriptional gene regulation involving small non-coding RNAs called miRNAs has also been discovered a few decades ago. These miRNAs are involved in the regulation of various genes in animal and plant system by upregulating and downregulating mRNAs [4]. With the escalating gene regulating complexity, it is fascinating to monitor and recognize a vibrant connection among small non-coding RNAs (miRNAs), transcription factors (TFs) and messenger RNAs (mRNAs).

MiRNAs are small non-coding (□22 nucleotides) RNA molecules present in viruses, plants and animals and are involved in post-transcriptional and post-translational regulation of gene expression. First miRNA molecule (lin-4) was discovered in *C. elegans* by Lee et al. [5]. Later on, second miRNA (let-7) was characterized by Reinhart et al. [6]. Both plants and animals undergo a similar biogenesis mechanism. A two-step procedure catalyzed by RNA pol III like enzyme is required in the miRNA processing of primary precursor. For further processing, these miRNAs are loaded into a protein complex known as RNA induced silencing complex (RISC) [4]. An open access miRNA database is managed by Griffiths-Jones Lab, University of Manchester (http://www.mirbase.org/index.shtml). This public database contains a total of 28,685 miRNAs from viruses, animals and plants [7] and is involved in regulation and modification of several biological pathways by controlling particular genes [8]. Therefore, identifying possible miRNA targets is an effective methodology to thoroughly study miRNA-mediated regulatory function at post-transcriptional level. Earlier studies carried out in Arabidopsis to explore some experimental parameters and procedures inferred for known miRNA-target interaction using bioinformatics tools have been utilized to reveal miRNA target genes in other plants [9]. Wet lab experiments like PAGE, Northern Blot, RAPD and Degradome sequencing were carried out to further validate the computational predictions [10].

Presently, 320,370 TFs have been identified from 58 families of 165 plant species [11]. Various repositories for plant TFs are available, which identify and collect TF from various plant species and are publically available for use (**Table 1**). MiRNAs and TFs are involved in upregulation and downregulation of the target genes, ultimately determine the destiny of specific gene, by turning "on/off" [12]. Mainly, miRNAs are involved in targeting DNA-binding proteins (TFs) [13]. Since a great impact on plant genetic system is exhibited by both the regulators, the interplay of miRNA-TFs will help in understanding the organization of several biological pathways.

Recently, miRNA-based research is focused on biotic and abiotic stress tolerance in plants. These stresses have a significant effect on plant growth and development and cause a great loss to yield. This chapter will provide deeper insights into miRNA-mediated gene regulation and their crosstalk with TFs, which will provide better understanding of plant responses to

Database	Acronym	Public URL	Description
Plant transcription factor database	PlantTFDB	http://planttfdb.cbi.pku.edu.cn/	PlantTFDB contains 320,370 TFs from 165 plant species
Arabidopsis thaliana—Plant transcription factor database	PlnTFDB	http://plntfdb.bio.uni-potsdam.de/v3.0/index.php?sp_id=ATH	PlnTFDB contains 2657 protein models, 2451 distinct protein sequences of *A. thaliana*
Database collection: Plant transcription factor database	PlantTFDB	https://www.ebi.ac.uk/miriam/main/datatypes/MIR:00000579	Systematically identifies TFs for plant species
Plant TFDB| Transcription factor data: Sequence database	PlantTFDB	http://planttfdb.cbi.pku.edu.cn/	A database of functional and evolutionary study of TFs
Pigeon pea transcription factor database	PpTFDB	http://14.139.229.199/PpTFDB/Home.aspx	Provides a range of information about pigeon pea TFs, encompasses about 1829 TFs and classifies them into 55 TF families
Phaseolus vulgaris transcription factor database	PvTFDB	http://www.multiomics.in/PvTFDB/	Provides comprehensive information about each of the identified TF, encompasses 2370 TFs and classifies them into 49 TF families
Chickpea transcription factor database	CicerTransDB	http://www.cicertransdb.esy.es/documents/about.html	Facilitates uses with a platform for unified and comprehensive study of chickpea TFs
Arabidopsis gene regulatory information server	AGRIS	http://agris-knowledgebase.org/	Provides information about Arabidopsis promoter sequences, TFs and their target gene
Arabidopsis thaliana transcription factor database	AtTFDB	http://agris-knowledgebase.org/	Contains information about 1770 TFs and group them into 50 families on the basis of conserved domains
Database of rice transcription factors	DRTF	http://planttfdb.cbi.pku.edu.cn/	2048 TFs have been identified and are grouped into 56 families from subsp. japonica
Rice stress-responsive transcription factor database	RiceSRTFDB	http://www.nipgr.res.in/RiceSRTFDB.html	Provides most comprehensive information about the expression pattern of rice TFs during drought and salinity stress conditions
Database of populus transcription factors	DPTF	http://planttfdb.cbi.pku.edu.cn/	4287 TFs have been identified and are grouped into 58 families
Database of maize transcription factors	DMTF	http://planttfdb.cbi.pku.edu.cn/	3308 TFs have been identified and are grouped into 56 families
Database of tomato transcription factors	DTTF	http://planttfdb.cbi.pku.edu.cn/	1845 TFs have been identified and are grouped into 58 families
Database of wheat transcription factor	wDBTF	http://wwwappli.nantes.inra.fr:8180/wDBFT/	It contains about 1127 predicted TFs from bread wheat
Stress-responsive transcription factor database	STIFDB	http://caps.ncbs.res.in/stifdb2/	It is a comprehensive collection of biotic and abiotic stress-responsive genes in Arabidopsis and rice

Database	Acronym	Public URL	Description
Transcription factor prediction database	DBD	http://www.transcriptionfactor.org/index.cgi?Home	DBD is a database of predicted TFs in completely sequenced genomes
Interspecies TF function finder for plants	IT3F	http://jicbio.nbi.ac.uk/IT3F/	Provides information about function of TFs

Table 1. Plant transcription factors database.

various biotic and abiotic stresses and will help in developing high yielding and stress tolerant varieties, which is the ultimate aim of the agricultural scientists.

2. Regulatory roles of transcription factors in plants

TFs genes are regulated at both transcriptional and post-transcriptional level in plants [14]. Therefore, to build regulatory networks, understanding the expression of TFs is of great importance. Mainly, TFs act by binding the *cis* element present inside the transcription initiation (promoter) region of their target gene [15]. Recent studies have shown that changes in gene expression are closely related with changes in expression of TFs [16] affecting growth and development in plants [17]. Manipulation of desired traits in plants by engineering TF genes is considered as a major future outlook [18].

Nuclear factor Y (NF-Y) is a class of transcription factor that has three subunits and all are vital for DNA-binding ability (NF-YA, NF-YB and NF-YC) [19]. The function of these TFs varies with the type of subunit. For example, NF-YA and NF-YB are involved in plant responses to drought stress, whereas NF-YC is involved in the regulation of flower development and light-mediated plant growth and development (photomorphogenesis) [20]. NF-Y transcription factors are also involved in plant-microbe interaction, root development and responses to stress [21]. Dark-grown phenotype was exhibited by *NF-Y* mutant plants even in the presence of light; this indicates that NFY TF is a positive regulator of photomorphogenesis [20]. In combination with NF-YB/NF-YC, NF-YA was found to be involved in flowering by triggering *FLOWERING LOCUS T* (FT) gene [22]. Overexpression of NF-YA5 in Arabidopsis resulted in tolerance to drought stress [23]. ABA disruptive phenotype was exhibited by *NF-YC* mutant Arabidopsis plants [24]. Nuclear factor Y complex binds with a unique *cis*-element within the SOC1 promoter region of Arabidopsis and regulates flowering time [25]. In Arabidopsis, leaf development is regulated by NF-YA2 and NF-YA10 via auxin signaling [26]. Arabidopsis nuclear transcription factor genes NF-YA1, 5, 6 and 9 play an important role in the regulation of male gametogenesis, embryogenesis and seed germination [27]. NF-YB confers drought tolerance and leads to improved yield in maize under water-limited conditions [28]. In Arabidopsis, NF-YC3, 4 and 9 are required for regulation of CONSTANTS (CO)-mediated photoperiod-independent flowering [29]. During the early seedling stage in Arabidopsis, under photomorphogenesis, hypocotyl elongation is suppressed by NF-YC1, 3, 4 and 9 [30]. Wheat *TaNF-YB3* gene imparts drought tolerance by regulating ABA-associated signaling pathway [31]. Overexpression of NF-YC9 confers ABA hypersensitivity in Arabidopsis [32].

MYB (myeloblastosis), a huge family protein, is characteristic of all eukaryotes and plays a diverse role in gene networking. Generally, MYB functions as transcription factor and their DNA-binding ability varies with the number of MYB domains [33]. In plants, MYB proteins are classified in four different classes depending upon the number of DNA-binding MYB domains: MYB-related, R2R3-MYBs, R1R2R3-MYBs and atypical MYBs [34]. The first plant MYB gene C1 was identified from maize [35]. Since their identification, they have been found to be extensively dispersed in plants and communicate with additional transcription factors [36]. MYB transcription factors are involved in the regulation of plant growth and development in various species like in soybean, they are involved in regulation of flower color [37] and regulation of signal transduction pathways in Arabidopsis, rice and cassava [38]. Biosynthesis of secondary metabolites is regulated in Arabidopsis and Medicago [36]. In Arabidopsis, sugarcane, potato, cotton, wheat, rice and *Camelina sativa*, they are involved in drought tolerance [39]. Chilling tolerance is imparted in Arabidopsis, wheat and rice [40]. MYB transcription factor genes are also involved in combating salt stress [41].

Arabidopsis transcription factor APETALA2 (AP2) is involved in the regulation of complicated processes of plant growth and development, which includes seed development, maintenance of stem cells and flower development [42]. APETALA2 family, also known as "A" class, acts together with B and C class to determine the final floral organ development, and this interaction of transcription factors forms the well-known ABC model of flower development [43]. Pandey et al. identified an APETALA2 (AP2) domain TF in Arabidopsis that suppresses ABA response during seed germination and ABA and stress-induced gene expression. They also observed that *abr1* mutant plants were hypersensitive to osmotic stress and higher level of ABA was found in mutant plants; this supports that ABA-mediated gene regulation is suppressed by AP2 [44]. Overexpression of *Nicotiana tabacum Tsi1* gene encoding an EREBP/AP2 TF in tobacco enhances resistance against osmotic stress and pathogen attack [45]. Overexpression of *WXP1*, an AP2 domain-containing TF gene of *Medicago truncatula*, enhances wax accumulation and drought tolerance in transgenic alfalfa [46]. Overexpression of *ORA59*, an AP2/ERF transcription factor domain, results in enhanced resistance against fungus *Botrytis cinerea* [47]. WIND1 and AP2/ERF TFs regulate cell differentiation in Arabidopsis [48]. WRINKLED1 (WRI1), an AP2-type transcription factor, was found to be associated with triacylglycerol (TAGs) accumulation in Arabidopsis [49].

TCF transcription factors comprise a domain, called TCP domain, which shares a motif that forms a basic helix-loop-helix (bHLH) structure that has DNA-binding properties [50]. The name TCP came from TEOSINTE BRANCHED1, CYCLOIDEA (CYC) and PROLIFERATING CELL NUCLEAR ANTIGEN FACTOR1 (PCF1) and PCF2, first four members of the TCP family derived from maize, snapdragon and rice, respectively [51]. Earlier studies have shown that TCP has been involved in the regulation of leaf formation by regulating cell cycle [52]. TCP transcription factors are also involved in flower development [53], leaf senescence [54], shoot development [55], jasmonic acid and auxin signaling [56], cell proliferation [57], leaf shape regulation [58], development of macro and micro [50], mitochondrial biogenesis [59] and regulating circadian cycle [60].

One of the largest and diverse families of plant regulators is WRKY transcription factors, with nearly 74 members in Arabidopsis, over 100 in rice, soybean and poplar [61]. There is at least one conserved DNA-binding domain called WRKY domain, which comprises a preserved protein

sequence (WRKYGQK) and a zinc-finger domain. Both of these sequences (hexapeptide and zinc finger domain) are required for binding to *cis* element known as W box (TTGACT/C) [62]. WRKY transcription factors are involved in several molecular and genetic pathways to regulate multiple responses simultaneously, whether it is abiotic or biotic stress [63]. Production of few secondary metabolites like lignin, flavanols and tannins is also regulated by WRKY TFs [64].

NAC transcription factors are one of the major class of plant regulators, engaged in stress responses. The name NAC is derived from three genes initially having the NAC domain; no apical meristem (NAM), Arabidopsis transcription activation factor (ATAF1/2) and cup-shaped cotyledon (CUC2) [65]. The availability of genome sequencing technology has led to the iden-tification of several NAC TFs genes in various species like 117 in Arabidopsis, 151 in rice, 79 in grape, 26 in citrus, 163 in poplar, 152 each in soybean and tobacco, 145 in cotton, 45 in tea plant, 172 in radish, 152 in maize and 110 in potato [66]. In Arabidopsis, of 10 NAC domains 9 domains bind to a conserved DNA target with a GGT[GA] core [67]. NAC TFs are mainly involved in the regulation of plant growth and development under biotic and abiotic stress [68].

Another important class of TFs that belong to plant kingdom is homeodomain-leucine zippers (HD-Zip). In Arabidopsis, there are more than 25 genes that encode these TFs. The HD-Zip protein is characterized by the presence of two important domains: a homeodomain (HD) involved in DNA binding and leucine zipper domain (Zip) responsible for protein-protein interactions [69]. On the basis of earlier sequence similarity findings, HD-Zip class of TFs has been grouped into four different classes (HD-Zip I, II, III and IV). Class I TFs (HD-Zip I) are engaged in ABA (abscisic acid) signaling, embryo development and responses to abiotic stress. Class II (HD-Zip II) TFs are involved hormone signaling (auxin), responses to light and shade. Likewise, class III (HD-Zip III) regulate embryo development, initiation of lateral organs, leaf polarity and meristem functioning, whereas class IV (HD-Zip IV) governs trichome develop-ment, root development, epidermal cell differentiation and accumulation of anthocyanin [69].

3. Interplay between transcription factors and miRNA

Plant miRNAs are involved in regulatory networks, which control differential gene expres-sion at tissue and developmental levels. MiRNAs and TFs provide combinatorial gene reg-ulation involving diverse functions which can further be exploited in crop improvement. Combination of microRNA and their targets, which are mainly transcription factors that depict an integrated image for designing regulatory relationship but it could be very difficult at times to develop a clear cut relationship as interaction could take place with each other leading to some novel regulatory pathway. With the advancement in bioinformatic softwares and use of advanced techniques, it is comparatively easy to develop an interaction. MiRNA and TFs are among the primary regulators of gene expression, thus affect plant phenotype in relation to growth and development (**Table 2**).

3.1. Root architecture

MiRNAs and TFs together govern the regulatory network involved in the development of root architecture in various species. In *A. thaliana*, miR160 is known to play key role in root growth

miRNA	TF family	Plant	Role
169	NY-FA	*A. thaliana*	Root architecture, nodule formation, drought and salinity stress, abscisic acid response
159	MYB	*A. thaliana*	Seed germination, senescence, ABA hypersensitivity
		O. sativa	
828 and 858	MYB	*G. hirsutum*	Fiber development, response to high temperature
164	NAC1	*A. thaliana*	Lateral root development
		Z. mays	
		T. aestivum	Contribute resistance against *P. striiformis f. sp. Tritici* (*Pst*)
396	GRF	*A. thaliana*	Leaf and grain development
		Z. mays	
		O. sativa	Response to arsenic treatment
	WRKY	*H. annuus* L.	Response to high temperature
319	TCP	*A. thaliana*	Leaf and floral development, jasmonic acid biosynthesis
164	NAC	*A. thaliana*	Lateral root development
	NAC1	*Z. mays*	Drought tolerance
166	HD-Zip III	*A. thaliana*	Shoot apical meristem, organ polarity and vascular development
156	SPL	*A. thaliana*	Floral development
		Z. mays	
		O. sativa	
		S. lycopersicum	
172	AP2	*Glycine max*,	Nodule formation
		P. vulgaris	
447 and 5255	MYB	*G. hirsutum*	Root and fiber development

Table 2. Differential role of TF-MiRNA interaction in plants.

by negatively regulating AUXIN RESPONSE FACTORs (ARF 10, 16 and 17) and resulted into shorter roots with tumor like puffed-up apex, if overexpression of miRNA160 occurs [70]. Apart from this, another miR164 targets transcription factors of the NAC (NAMATAF-CUC) family and regulates lateral root initiation by limiting NAC1expression [71]. Similarly, in legumes such as *M. truncatula*, miR166 and HD-Zip regulate cell-to-cell communication in root vascular and meristematic tissues [72]. In *A. thaliana*, miR169 isoforms are engaged in targeting NF-YA TF and control primary root growth. The prevention of miR169 expression affects lateral root initiation led to altered dimensions in root meristem [73]. The cross talk between miR166/165 and their target HD-Zip III ensures root development in *Arabidopsis thaliana* as well as in Maize.

3.2. Phosphate content

Phosphorus is essential nutrient for plants and can be acquired by plants only as inorganic phosphate. Certain transcription factors, such as AtPHR1, AtWRKY75, AtZAT6 and

AtBHLH32, regulate phosphate starvation responsive genes in plants. The interplay between miR399 and transcription factor AtMYB2 is known to function in abiotic stress signaling in Arabidopsis, and overexpression of AtMYB2 results into increased phosphorous uptake and changes in root architecture [39].

3.3. Leaf senescence

Leaf senescence is a physiological process, which affects vegetative and productive developmental processes in plants. Increased seed yield and prolonged life span are observed during delayed. The conversion, which occurs from leaf maturation to senescence, is complex and is associated with several genes and transcription factors such as MYB, SQUAMOSA PRMOTER BINDING-LIKE (SPL), WRKY, etc. [74]. Transcription factor MYB was targeted by zms-miR 159d and was downregulated in maize inbred line ELS-1, whereas in Yu87-1inbreed line, zms-miR 159d was found to be upregulated [75].

3.4. Fiber development

Various studies have reported that different transcription factors play an important role in fiber initiation. For example, MYB transcription factors are involved in fiber trichome development in cotton. TFs are predicted to be targeted by certain miRNAs such as MYB3 and MYB88 are targeted by miR447, which is significantly expressed during different fiber initiation, elongation and secondary wall synthesis and play important role in fiber development under salinity and drought stress [76]. In a recent study, MYB genes, including MYB2, MYB3 and MYB12, are targeted by miR828 and are known to play negative role in fiber elongation [77].

3.5. Floral development

Different microRNAs function and play role throughout flower development from early stages to late stages. These microRNAs target various transcription factors by targeting and downregulation and affect floral timing [78]. There are around 11 different miRNA families (miR156, miR159, miR160, miR164, miR165/miR166, miR167, miR169, miR172, miR319, miR390 and miR399) that regulate flower development at several stages. MiR156, miR172 and miR399 mediate plant changes from juvenile to adult, whereas mR159, miR169, miR172 and miR399 mediate transition from vegetative to adult. MiR156 controls flower development in rice, tomato and maize, and its role is found to be conserved [78]. The targets of miR156 are SPL (SQUAMOSA PROMOTER BINDING-LIKE) TFs, which are being downregulated in Arabidopsis, and miR172 targets expression of APETELA2, which resulted in delayed flowering by inhibiting translation [79].

3.6. Nodule formation

Nodule formation and establishment of symbiotic relationship are complex processes. Various miRNA and transcription factors are associated with nodule development. It was suggested that miR169-mediated repression of MtHAP2, a transcription factor, was required for nodule

development in *M. truncatula* [76]. In legumes, such as soybean and common beans, miR172 interacts with AP2 TFs to regulate nodule organogenesis [80].

3.7. Leaf morphogenesis and grain filling

MicroRNA and TFs play a vital role in leaf morphogenesis such as miR319 and TCP are involved in regulation of leaf size. Increase in leaf size was observed with loss of function of miR319 [81]. Similarly, miR319 overexpression resulted in enlarged leaf formation in tomato [82]. Another miRNA family (miR396) targets GRF (GROWTH-REGULATING FACTOR) TF family and regulates leaf morphogenesis [83]. Cell division in leaves is enhanced by suppression of six GRF genes and GIF1 by overexpression of miR396 [83]. MiR396 and GRF TFs are found to be associated with effective grain filling in maize [84]. Similar findings were observed in rice where LOC_Os02g47280 was downregulated by miR396 and was found to be responsible for grain shape [85]. These studies approved the networking between miR396 and GRF transcription factor and suggested the strong role in leaf development and grain filling.

3.8. Shoot apical meristem and vascular patterning

Plants exhibit a long period of organogenesis and give rise to new leaves throughout their life cycle depending upon the activity of shoot meristems. The transcripts of miR165 and miR166 are detected in shoot apical meristem, leaf primordial and vascular tissues in Arabidopsis. The interaction of HD-Zip III with miR165 and miR166 is well known [86]. It regulates diverse functions including plant development, apical and lateral meristem formation, vascular growth and leaf polarity. Downregulation of three HD-Zip genes (ATHB-9/PHV, ATHB-14/ PHB and ATHB-15) resulted into recapitulate phenotype upon overexpression of miR166. Similarly, downregulation of five HD-Zip genes by overexpression of miR165 resulted in loss of SAM (shoot apical meristem), changed organ polarity and defected vascular development [87]. MiR165 and miR166 are involved in the regulation of leaf asymmetry patterning in maize and Arabidopsis. The suppression of HD-Zip by miRNA is responsible for vascular patterning in leaves and stem in both monocots and dicots [86].

3.9. Flavonoid biosynthesis pathway

In Arabidopsis, miR858a is supposed to target R2R3-MYB transcription factor. Genomic analysis suggested that miR858a targets various regulatory factors involved in plant growth and development. Overexpression of miR858a led to downregulation of several MYB transcription factors, which in turn regulates and redirects the metabolic flux towards flavonoid biosynthesis [88].

3.10. Jasmonic acid biosynthesis

Jasmonic acid (JA) acts as systemic signaling molecule, which is effective against tomato root knot disease (RKN). This can reduce the number of root knots from nematode invasion resulting into JA-mediated RKN resistance in roots. Several miRNAs are found responsive

to jasmonic acid against pathogen infection. Recent study demonstrated negative correlation between miR319 and its target TCP4 in tomato using reverse genetic approaches. This interaction leads to change in levels of jasmonic acid in leaves. The potential cross talk between miR319 and TCP4 modulates systemic defensive response [89].

3.11. High temperature tolerance

An environmental fluctuation such as high temperature imparts detrimental effect on plants. Some plants show tolerance to these stresses than others and are regulated by a wide network of transcriptional cross talk between transcription factors such as WRKY, ERF, NAC, MADS and miRNA. WRKY TFs found most exclusively in plants and are involved in various developmental and physiological processes. When plants are exposed to high temperature or salicylic acid in case of sunflower, opposite expression of HaWRKY6 and miR396 was observed [90]. In case of cotton, MYB transcription factor is known to be upregulated against high temperature and was targeted by miR828a and miR858 [91].
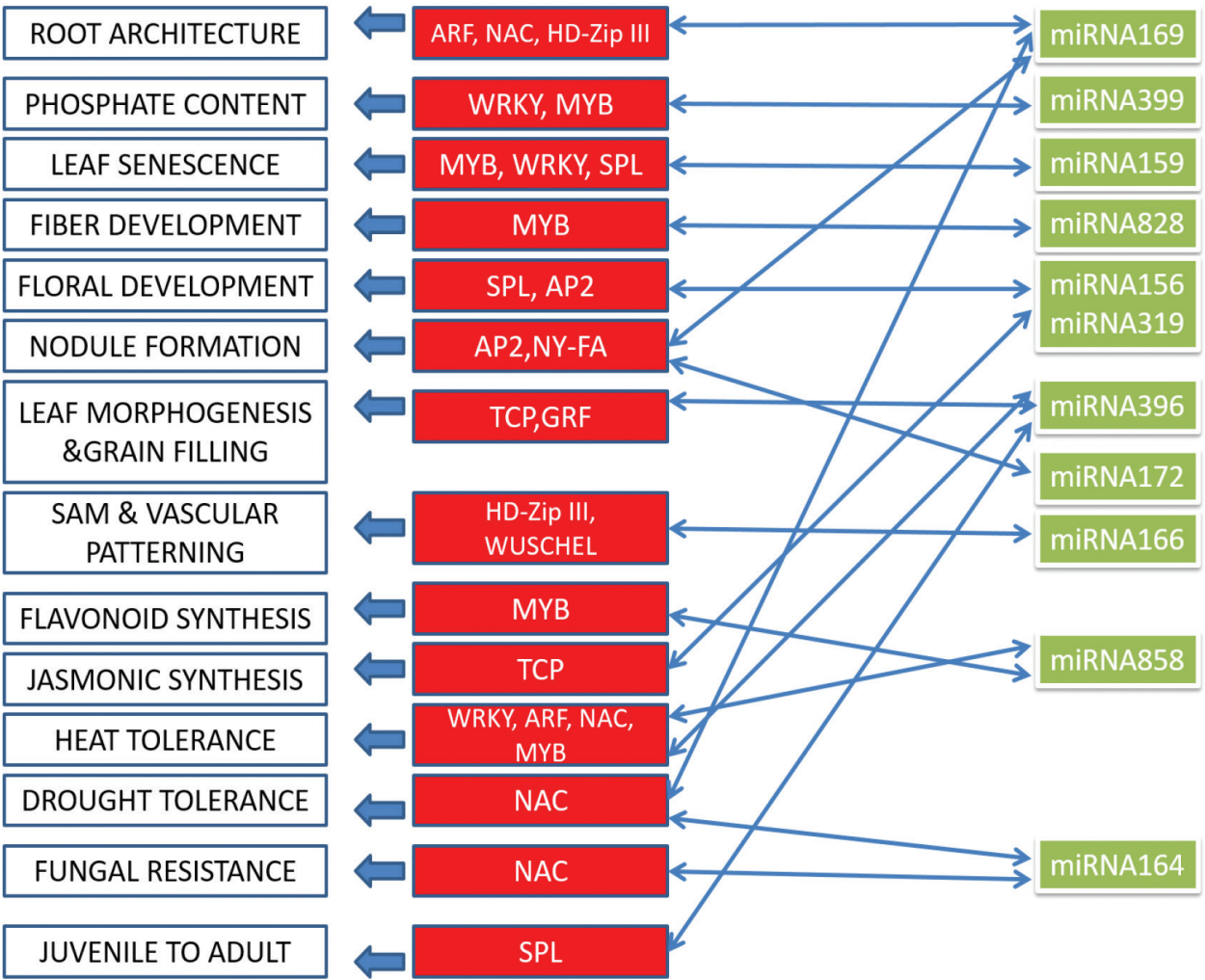

Figure 1. Interaction between miRNAs and TFs for gene regulation in plants.

3.12. Drought tolerance

Communication between miR164 and NAC TF genes confer negative regulatory role in drought resistance in rice in addition to developmental roles. In transgenic Arabidopsis plants, overexpression of miR169a in NF-YA5 mutants resulted in increased susceptibility towards water stress in comparison to wild-type plants. Enhanced drought tolerance was observed in plants overexpressing NF-YA5. In addition to drought tolerance, miR169 is also related with salt stress [92]. This phenomenon was also observed with miR393 [93].

3.13. Fungal pathogen resistance

The molecular crosstalk between miRNA and transcription factor is necessary to better understand the disease development. In wheat, stripe rust caused by Puccinia is a serious disease occurring during growing season. Crosstalk between miR164 and NAC21/22 TF resulted into reduced stripe rust resistance. These results conclude that mir164 and novel transcription factor are imperative in the development of stripe rust resistance in wheat [94].

3.14. Juvenile to adult plant development

The conversion from juvenile to adult is accompanied by changes in vegetative morphology and increase in reproductive potential. The regulatory mechanism of this transition involves miR156, miR172 and SPL gene family in case of Arabidopsis. SQUAMOSA PROMOTER BINDING-LIKE (SPL) TF family is a major target of miR156, and 11 SPL genes are repressed through translational inhibition and mRNA cleavage [95]. MiR156 and miR172 are positively regulated by transcription factors they target, and negative feedback loops contribute to stability of juvenile and adult phases (**Figure 1**) [79].

4. Conclusion

Regulatory network involving TFs and miRNA provides deep insight in understanding the complexity of gene regulation in plants. Till date, the computationally and experimentally mapped networks portray considerable information on gene regulation. The complete spectrum of miRNA and their interactions with transcription factors need to be considered in order to study regulatory interactions at particular developmental times or in a tissue specific manner. However, it will be imperative to incorporate all accessible miRNA, TF and target expression blueprint to confine the network to just those communications that can happen and to extend the studies in different set of conditions. For the computational researchers, the particular issues will be to gather and analyze the accessible information, make predictions and to approve the speculations in view of literature or wet lab experiments for set up of regulatory network. In near future, better understanding of regulatory networks is expected, which will enable us for manipulating gene expression for crop improvement and industrial applications. At present, it is, by all accounts, a difficult work to build complete real-time networks

for more experimental information. Still, it is a long way to establish complete miRNA-mediated regulatory network in plants.

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