

Short Communication

Transcription Factor: Current and Future Perspectives

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Differential gene expression is an essential response in plants under abiotic stresses [1]. In response to abiotic stresses such as, drought, salinity, heat, cold and mechanical wounding many genes are regulated, and their gene products function in providing stress tolerance to plants. Understanding the molecular mechanisms of plant responses to abiotic stresses is very important as it facilitates in exploiting them to improve stress tolerance and productivity [2].

The cells of higher organisms exhibit various genetic responses to their surrounding environment. This is because of the involvement of Transcription Factors (TFs) that regulate the way through which genes are transcribed. TFs control various aspects of organismal development while TF signals can control over DNA by allowing for gradations of expression. TF families further enhance the genetic complexity in eukaryotes, and many TFs within the same family often work together to affect transcription of a single gene [3]. While, differential expressions of TFs/regulators are another important mechanism that further regulates the expression of various genes under these environments [1]. Understanding these regulatory hierarchies of gene expression networks in response to developmental and environmental cues is a major challenge due to the complex interactions between the genetic elements [4]. The expression of genes is regulated by a number of TFs. Role of important plant TFs namely; ABRE, MYC/MYB, CBF/DREBs and NAC that regulate the expression of various stress responsive genes in providing tolerance to multiple stresses generally in both ABA dependent and ABA independent manner and through their respective *cis*-elements and DNA binding domains has been described [2].

As rice paddies are the major methane source for the production of atmospheric methane. And to establish sustainable technologies for increasing rice production while reducing methane fluxes from rice paddies, a report recently came indicating that addition of a single TF gene, barley *SUSIBA2*, conferred a shift of carbon flux to *SUSIBA2* rice, favouring the allocation of photosynthates to aboveground biomass over allocation to roots. The altered allocation resulted in an increased biomass and starch content in the seeds and stems, and suppressed methanogenesis, possibly through a reduction in root exudates [5]. The basal TF IIA gamma subunit TFIIAg5 from rice is a key component for infection by the TALE-carrying bacterium *Xanthomonas oryzae* pv. *oryzae*, the causal agent for bacterial blight

[6]. Also NAC (NAM/ATAF/CUC) TFs comprise a large plant-specific gene family having more than 149 members in rice. Extensive studies revealed that NAC TFs not only play important roles in plant growth and development, but also have functions in regulation of responses to biotic and abiotic stresses [7]. Recently an approach to develop drought tolerant peanut genotypes under drought by genetic engineering the ruling peanut varieties using TF regulating the expression of several downstream, abiotic-stress responsive gene(s) has been reported [8].

TFs play key roles in the regulation of genes involved in normal development as well as tolerance to biotic and abiotic stresses [9]. TFs provide nodes of information integration by serving as nuclear effectors of multiple signaling cascades, and thus elaborate layers of regulation, often involving post-translational modifications, modulating and coordinate activities [10]. Functional conservation and diversification of TFs across monocot and eudicot lineages are reported [11]. Although role as well as mechanism of known TFs is being worked out. However, there are sets of TFs about that no study has been carried out. Taking this into account an initiative to recognize least studied TF/regulator genes in rice was performed by accessing the Plant Transcription Factor Database and Rice Oligo Array Database on the basis of PCC (Pearson Correlation Co-Efficient) cut-off value in the co-expression network analysis. By comparative analysis and evolutionary relationship of these TFs/regulators total 39 TFs genes were identified having least information and belonging to 11 different TFs families and 7 transcription regulators in rice [12]. Comparative analysis of TFs in rice and Arabidopsis was also performed where comparable to the 1510 TFs of *Arabidopsis* total 1611 TF genes belonging to 37 gene families in rice were identified [11]. Structure, function and networks of TFs involved in abiotic stress (including drought, high salinity, high osmolarity, temperature extremes and ABA) responses has been reviewed [13] emphasizing on seven major TF families (basic leucine zipper, bZIP; APETALA 2/ethylene-responsive element binding factor, AP2/ERF; NAM/ATAF1/CUC2, NAC; WRKY; MYB; Cys2(C2)His2(H2)-type zinc fingers, ZFs; and basic helix-loop-helix, bHLH). Arabidopsis WRKY super family of TFs has been elucidated previously [14,15] and WRKY TFs are known to play a key role in plant-specific processes such as trichome development and the biosynthesis of secondary metabolites, regulating the pathogen-induced defense mechanism as well as their extension during the evolution under wide variety of biotic and abiotic stress responses [15]. Earlier a genome wide analysis of chromosomal distribution, tandem repeats and phylogenetic relationship of MYB TFs family genes in rice and Arabidopsis were reported [16]. Recently an extensive study on MYB TFs i.e. one of the largest TF families that regulates defense responses to various stresses, hormone signaling as well as many metabolic and developmental processes in plants has been carried out [4]. Transcription Activator-Like Effectors (TALEs) that are sequence-specific DNA binding proteins found in a range of plant pathogenic bacteria where they play important roles in host pathogen interactions has also been described [6].

Variation in TF expression or its activity will affect more than one downstream modification as TFs are hierarchically higher and have the ability to regulate many downstream targets [17]. Impact of post-translational modifications in ETS TFs affecting its various activities including subcellular localization, stability, interactions with cofactors, etc. has been reviewed [18]. Expression of genes coding for components regulating many aspects of photosynthetic metabolism that is affected by stress, and TFs have a substantial role in regulating them and thus carbon metabolism has been reported [19]. Study to analyze the diversity in the promoters of 24 TFs families and regulation mechanism of varied drought tolerance among 95 rice genotypes using the Ecotype Targeting Induced Local Lesions in Genomes (Ecotilling) method has also been carried out [20]. Recently transcriptome data for comprehensive regulatory network studies of MYB TFs by “top-down” and “guide-gene” approaches while clusters identification using Markov Clustering (MCL) has been also reported [4]. Also, research progress on the function of WRKY TFs in rice disease resistance indicating the selection of candidate WRKY genes for characterization and evaluation in transgenic strategies for disease resistance development in rice has been reviewed [21]. Eight TFs/regulator genes were used to study their differential expression pattern in some susceptible and tolerant rice cultivars by imposing different abiotic stresses (drought and submergence). Result revealed that expression of *Arabidopsis* RESPONSE REGULATORS Type-B (ARR-B), Vascular plant One Zinc finger protein (VOZ) and GLABROUS1 enhancer-binding protein (GeBP) genes families varies during the different stress conditions [1]. Expression pattern of various TFs using drought tolerant and susceptible peanut genotypes was studied. Here 12 putative TFs were analyzed using real-time PCR resulting three unique transcripts in which ahERF1 was highly induced in the recovery stage; ahERF7 and ahERF8 were also highly induced by drought and re-turned to nominal levels after recovery. These sequences contain DNA binding domains that are present in the APETALA2/Ethylene Responsive Factors (AP2/ERF) family of TFs and known to be induced by stress [9]. Recently a report indicating eight independent transgenic peanut (cv. GG20) lines were developed using *AtDREB1A* gene, encoding for a TF, through *Agrobacterium*-mediated genetic transformation. The transgenic plants at 45-d or reproductive growth stage showed tolerance to severe soil-moisture deficit stress. While physio-biochemical parameters were found positively correlated with growth-related traits without any morphological abnormality, when compared to wild-type. Real Time PCR analysis revealed consistent increase in expression of *AtDREB1A* gene under progressive soil-moisture deficit stress in two homozygous transgenic plants [8].

Specific DNA binding and specific gene regulation has been reviewed describing that recognition of motif/*cis*-regulatory regions is mandatory for gene regulation in response to developmental and environmental signals. The pathways in which TFs recognizing similar consensus sites distinguish their own targets from a large number of other sequences to ensure specific cellular responses [22]. Upstream activation sequence and promoter structure, TF classification, examples of regulated TF activity, understanding the RNA polymerase II transcription machinery, conserved coactivator complexes, transcription activation domains, and the cooperation of TFs in gene regulatory mechanisms has been elucidated in

Saccharomyces cerevisiae well [23]. TFs recognizing specific DNA sequences, the evolution of TF families, complexity of TF about their occurrence has been reported [3]. Characterization of the target sequence specificity of 63 plant TFs representing 25 families, using protein-binding microarrays has been reported [24]. Interactive nature of TFs with DNA sequence to resolve information-energy tradeoff has also been described [25]. In gene regulation the transcriptional regulation is governed by the recognition of *cis*-element by the DNA binding domain of TFs. The assembly of TFs on the promoter *cis*-element region and their interaction in regulatory network profoundly influence the target gene expression [4]. Genes with similar expression pattern in the same biological function are likely to be regulated by same TF(s) (i.e., co-regulated) having similar *cis*-regulatory elements for the TFs were liable for putative target gene identification [26-29]. Another extensive review on regulatory architecture (covering core promoter architecture and basal transcription machinery, key regulatory modules for constitutive expression of rice genes, stress response and hormonal signaling, tissue/organ-specific gene expression, and *cis*-element and TF databases etc.) of rice gene has been done [30]. Regulatory mechanism in rice during anoxia was studied by identifying and validating the promoter motifs through Molecular Beacon Probes (MBP) based Real Time PCR and its subsequent *in silico* protein-DNA interaction study between motif and Sub1A [31] and APETALA2/Ethylene-responsive element binding proteins (AP2/ERBP) [32] using computational approaches.

Responses and adaptations required differential gene expression that is regulated by specific TFs [19]. TF coding sequence variation can change the expression of a subset of downstream target genes without wholesale disruption of the entire downstream gene hierarchy. These changes in TF can result in gaining new functions while maintaining their overall role [33,34], or acquiring an entirely new role; or in some cases this is correlated with the gain or loss of known interaction motifs [35,36]. Evolution of new functions by orthologous TFs have been discussed indicating that variation in TF protein sequence can affect the regulation of only a subset of target genes, even in the same cells [37]. Several TFs regulating stomatal aperture and mediating responses to adverse environmental conditions has been elucidated [19]. Also, several TFs belonging to the MYB family play an important role in both stomatal and non-stomatal responses by regulation of stomatal numbers and sizes, and metabolic components, respectively [19]. TFs regulate gene expression by binding with motif/*cis*-regulatory specific sequences present in the promoters of their target genes [24]. Candidate gene screening and experimentally testable hypotheses for potential regulatory MYB TFs, and their targets under stress conditions has been recently reported [4]. Adaptation of the binding interaction towards increasing information transfer under a general energy constraint implies that the information gain per specific binding energy at each base-pair is maximized and suggesting that adaptation of information gain is a generic design principle of molecular recognition systems [25]. *OsGRAS23* gene encoding stress-responsive GRAS TF positively modulates rice drought tolerance via the induction of a number of stress-responsive genes while yeast one hybrid test based result indicated that *OsGRAS23* could bind to the promoters of its potential target genes [38]. *OsWRKY47* TF that work as a positive regulator during drought stress in rice has been studied

[39]. Further, considering the regulatory mechanism in plant's flowering time during external factors such as water availability, and utilizing a large-scale hybrid TF approach Zhang et al. [40] has identified a bZIP TF, *O. sativa* ABA responsive element binding factor 1 (OsABF1) that acts as a suppressor of floral transition in a photoperiod-independent manner. During subsequent study a drought-inducible gene namely *OsWRKY104* was identified that is under the direct regulation of OsABF1. Also, regulation of gene expression by TFs helps plant pathogens to interact with the host plants and to sustain a pathogenic lifestyle in the environmental changes. Considering this Chung et al. [41] studied two Zn(II)2Cys6 TF genes (MoCOD1 and MoCOD2) in the rice blast fungus and reported that both TFs play important roles in conidiation and pathogenicity of the rice blast fungus.

Positive and negative regulation of endogenous protooncogenes (*erbB-2* or *erbB-3*) expression by designed zinc finger TF proteins that bind 18-bp DNA sequences in the 5'untranslated regions of these genes was studied mentioning that regulation of the two genes was highly specific, despite the fact that the TF binding sites targeted in *erbB-2* and *erbB-3* share 15 of 18 nucleotides [42]. Role of the TFs (including AP-1, AP-2alpha, CREB, CtBP, ETS-1, HMGB1, LEF/TCF/ β -catenin, MITF, NF κ B, PAX3, SKI, Snail and STAT) in carcinogenesis emphasizing on melanoma development and progression has been reviewed previously [17]. Recently advances on TFs as drug targets in oncology, with an emphasis on the emerging chemical approaches to modulate TF function has been reviewed [43] suggesting that TFs as therapeutic targets for drug discovery. Repression of *erbB-2* in SKBR3 breast cancer cells inhibited cell cycle progression by inducing a G1 accumulation, suggesting that designed TFs has potential for cancer gene therapy [42].

Grass Regulatory Information Server (GRASSIUS) is a public web source having information of databases, computational and experimental resources related to gene expression regulation in grasses and their association with agronomic traits (<http://grassius.org/index.html>). Interaction of TF and promoter motif/*cis*-regulatory elements is being updated at GRASSIUS. GRASSIUS works as a "one-stop" resource in helping plant scientist and researchers for discovering the mechanism involved in the regulation of genome-wide gene expression. Whereas, Grass TFDB is a TF database that provide detailed information about the TFs from maize, sugarcane, sorghum, rice and brachypodium (<http://grassius.org/grasstfdb.html>). The Rice Stress Responsive Transcription Factor Database, Rice SRTFDB (<http://www.nipgr.res.in/RiceSRTFDB.html>) provide information about the expression patterns of rice TFs during water deficit and salinity stress conditions and various stages of development. *Cis*-regulatory elements located in the promoters of TFs and Tos17 mutant information could also be retrieved from the above database. YEASTRACT (Yeast Search for Transcriptional Regulators and Consensus Tracking available at <http://www.yeasttract.com>) is an important source of more than 206000 regulatory associations between TFs and target genes in *Saccharomyces cerevisiae*. It also includes the description of 326 specific DNA binding sites shared among 113 characterized TFs [44].

Expression pattern data of TFs/Regulator might be useful in determining their role in regulating the expression of various genes

as well as in co-expression networking analysis [1]. Some important TFs can be used for the production of transgenics that might have higher tolerance to drought, salinity, heat and cold stresses. Study on these TF genes in breeding and other crop improvement programs will provide an understanding about abiotic stress related signal transduction events, regulatory networks and their cross talk during stress adaptation [2]. Similar to strategy adopted by Sarkar et al. [8] drought or other stress tolerant legumes may be developed by looking some important TFs. To get more insight and large agronomic impact there is need to functionally characterize new TFs that mediate the stress responses regulating the expression of genes associated with photosynthesis (stomatal and non-stomatal) and related metabolism. However, obtained results must be carefully analyzed as few photosynthetic parameters are usually evaluated during this process and the growth/stress conditions are normally different from natural field conditions [19]. Further, it need to study that what extent changes in the amount of a TF can be buffered by nonfunctional binding, the recruitment of TFs to regulatory regions centers around nuclear architecture as well as the subtle dynamics that fine-tune gene regulation [22]. Identifying TFs associated with drought tolerance using the Ecotilling method may be useful in the drought tolerance breeding program based on germ plasm with distant genetic relations, by which the genetic diversity of modern varieties can be broadened [20]. Approaches to increase rice productivity and reduce methane emissions as seen in *SUSIBA2* rice may be particularly beneficial in a future climate with rising temperatures resulting in increased methane emissions from paddies [5]. Looking to the events seen it will be interesting to know whether changes in expression pattern have typically occurred before protein functional divergence or vice versa [37]. Gene-expression of ahERF1, ahERF7 and ahERF8 may be used to select plants that may have higher drought tolerance [9]. Correlation between *cis*-regulatory elements and the sequence determined *in vitro* using the protein-binding microarray will provide a framework to explore regulatory networks in plants [24]. Further, fine-tuning of the expression of key TFs for stress tolerance in specific temporal and spatial patterns to avoid negative effects in growth and yield need to be carried out [13]. Savir et al. [25] work provides a design principle for understating the shaping of discrimination energy profiles of other sequence-binding proteins in nature and in artificial settings. A way formulating a widely applicable strategy to improve resistance of plants to TALE-carrying pathogens need to be carried out [6]. The detailed mechanism for multiple layers of cooperativity and/or competition among different post translational modifications in TFs during response to distinct upstream signals yields immense regulatory opportunities that the cell almost certainly taking advantage need to be worked out [18]. *AtDREB1A* transgenic peanut plants [8] can be used further for the multi-year, multi-location trials under real-field conditions. Subsequently, the best one(s) can be used in the breeding programmes either as pre-breeding resources or directly as enhanced drought-tolerant genotype for commercial cultivation. Designing of TFs may be useful in gene therapy and in basic and applied research where alteration of gene transcription can be applied to dissect biological mechanisms or to alter phenotypes of cells and organisms [42]. Elucidating the functional roles of Zn(II)2Cys6 TF genes on fungal developments would provide new insights on deciphering molecular mechanisms of fungal pathogenicity on plants [41]. On

the other hand, understanding of regulating mechanisms of TFs can give important insight into melanoma development as well as in tumorigenesis for innovative therapeutic solutions [17].

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