

Role of HD-Zip transcription factors in plant development and stress responses

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Abstract

The HD-Zip transcription factors are unique to the plant kingdom. These proteins exhibit both a homeodomain with an adjacent leucine zipper motif in a single combination which is unique in all eukaryotes. They can be divided into four subfamilies, depending on some characteristic features which include their respective DNA-binding specificities, gene structures, presence of additional common motifs and physiological functions. HD-Zip proteins exist in almost all tissues and organs of higher plants. They mainly participated in plants growth, development, morphological formation, regulation of biotic and abiotic stress responses and modulate the action of hormones. Here, we make an effort to review recent experimental evidences explored for this family of transcription factors from a wide variety of plant species to unravel their pivotal function in various important aspects related to plant growth, development and adaptation to environment.

Highlight

- Plant HD-Zip transcription factor, a unique plant specific gene family, plays pivotal role in regulating multiple aspects of plant development as well as various stress responses.

Keywords: Abiotic stress, biotic stress, Hd-Zip family, light signalling, plant development, transcription factor

Several Transcription factor (TF) families consist of proteins that contain a DNA-binding domain known as the homeodomain (HD), named after a fundamental developmental reorganization called homeotic effect, which is caused by the mutation or ectopic expression of these genes (Garber *et al.*, 1983). The first HD-containing TF was identified in *Drosophila melanogaster* (Garber *et al.*, 1983). Proteins with highly conserved HDs have been found in wide range of members of animals, fungi and plants, indicating the importance of these TFs in developmental pathways across different kingdoms (Gehring *et al.*, 1994, Chan *et al.*, 1998, Khaled *et al.*, 2005). However, none of the known plant HB-

containing genes exhibit any such homeotic effect. The first HD-containing genes were discovered by Erik Volbrecht and coworkers in maize. The gene called *KNOTTED1*, was isolated from maize (*Zea mays L.*) (Volbrecht *et al.*, 1991). Since then, a large number of plant HD-containing TF genes have been isolated from different plant species. Based on the presence of specific functional domains, plant HD-containing TFs were classified into six families: (a) homeodomain leucine zipper (HD-Zip); (b) plant homeodomain with a finger domain (PHD); (c) Bell domain (Bell); (d) zinc finger with homeodomain (ZF-HD); (e) Wuschel homeobox (WOX); and (f) Knotted homeobox (KNOX) (Ariel *et al.*, 2007).



The HD-Zip family of TFs is exclusively found in plant kingdom, suggesting their involvement in plant specific developmental processes (Ruberti *et al.*, 1991, Riechmann *et al.*, 2000). A homeobox (HB) encodes a protein domain, the homeodomain (HD), which is a conserved 60-amino acid motif that folds into a characteristic three-helix structure. α -helix 3, considered the recognition helix, is the most conserved across HD proteins (Gehring *et al.*, 1994) and acts as determinants for protein–DNA interaction specificity. In contrast, a leucine zipper is a α -helix comprised of seven amino acid (heptad) repeats.

The HD-Zip family consists of four subfamilies or classes. A common feature of all four subfamilies is the presence of a leucine zipper domain (Zip) adjacent to DNA binding HD, which promotes homo- and hetero-dimerisation, a pre requisite for DNA binding (Ariel *et al.*, 2007). In this review we will shed light on the distinguished yet multi dimensional role employed by the members of all four sub classes during plant growth, development and stress responses.

Class I:

Arabidopsis HD-Zip I subfamily has 17 members (*ATHB1/HAT5*, *ATHB3/HAT7*, *ATHB5–7*, *ATHB12*, *ATHB13*, *ATHB16*, *ATHB20–23*, *ATHB40*, *ATHB51–54*) (Henriksson *et al.*, 2005). The genes of HD-Zip I share a common pattern of intron/exon distribution which is in good agreement with their phylogenetic relationships (Henriksson *et al.*, 2005). The encoded proteins are of ~35 kDa, and exhibit a highly conserved HD, a less conserved LZ with no additional domains (Chan *et al.*, 1998). It recognize the following pseudo pallindromic sequence: CAAT(A/T)ATTG. The HD-Zip I genes have been demonstrated till date, to play important roles in sugar signaling, abiotic stress, plant embryogenesis and de-etiolation (Henriksson *et al.*, 2005, Harris *et al.*, 2011). For example, Arabidopsis *ATHB5*, 6, 7, and 12 abundantly expressed under dehydration stress and upon ABA application and has been proposed to act as growth regulators in response to drought conditions (Lee and Chun, 1998; Soderman *et al.*, 1999; Hjellström *et al.*, 2003; Johannesson *et al.*, 2003; Olsson *et al.*, 2004). Analyses of plants ectopically expressing *ATHB1*, 3, 13, 20, or 23 suggest that these HD-Zip I genes participate in the regulation

of cotyledon and leaf development, and *ATHB13* potentially acts as a mediator of sugar sensing and responses (Aoyama *et al.*, 1995; Hanson *et al.*, 2001).

The Arabidopsis HD-Zip I gene *AtHB52* also shows a strong up-regulation of transcript level in response to blue light and darkness (Henriksson *et al.*, 2005). The sunflower (*Helianthus annuus*) *Hahb-4*, encoding the sunflower HD-Zip I protein, was identified as a developmental regulator which is also strongly induced by ethylene (ET), drought, herbivory, wounding, methyl jasmonate (MeJA) like stimuli (Dezar *et al.*, 2005; Manavella *et al.*, 2006, 2008). A recent report by Cabello *et al.*, (2012) revealed a conserved mechanism related to drought-, salt- and freezing-mediated enhancement without yield penalty by employing two homologous Hd-Zip I gene, *HaHB1* and *AtHB13*, from sunflower and Arabidopsis respectively. These two proteins confer plant tolerance to multiple abiotic stresses by inducing the proteins able to stabilize cell membranes. *Oshox22*, a rice HD-Zip homolog has been identified as a regulator of ABA biosynthesis with a positive regulatory role in drought and salt responses through ABA-mediated signal transduction pathways (Zhang *et al.*, 2012).

In tomato (*Solanum lycopersicum*), silencing of *H52* conferred spontaneous cell death in leaves, activation of defence genes, over production of ET and conjugated salicylic acid (SA), and growth suppression of virulent pathogens (Mayda *et al.*, 1999). The silencing of another HD-Zip I gene in tomato, *LeHB-1*, reduces *LeACO1* (ACC oxidase I) expression in fruits and inhibits ripening (Lin *et al.*, 2008). *NaHD20*, a *Nicotiana attenuata* γ -clade homolog, is also induced in roots and leaves upon exogenous ABA application and soil water deficit conditions (Re' *et al.*, 2011). In the resurrection plant *Craterostigma plantagineum*, the transcripts of *CpHB3*, 4, 5, 6 and 7 (type I HD-Zips) can be up or down regulated during dehydration in both leaves and roots (Deng *et al.*, 2002). *Medicago truncatula* HD-Zip I protein, *MtHB1*, was reported to be expressed in primary and lateral root meristems and also induced by salt stress (Ariel *et al.*, 2010). Recent progress showed that maize (*Zea mays*) HD-Zip I proteins also participate in abiotic stress (Zhao *et al.*, 2011). More recently, a particular HD-Zip gene from maize, *Zmhdz10*, has been reported to execute abiotic stress tolerance, when overexpressed both



in rice and *Arabidopsis* (Zhao *et al.*, 2014). All the above evidences reflect the potential importance of HD-Zip I proteins in context of plant growth and responses to adverse environmental conditions.

Class II:

This subfamily members exhibit two introns within their HD sequence. The HD and LZ domain conservation are alike the other classes. But this sub family contains two additional motifs: the CPSCE (named after the five conserved amino acids Cys, Pro, Ser, Cys, Glu in the one letter code) adjacent to and downstream of LZ, with an N-terminal consensus sequence (Chan *et al.*, 1998). The CPSCE domain is responsible for redox cell state sensing. This suggests that the activity of HD-Zip II proteins might be regulated by redox equilibrium state of the plant body (Tron *et al.*, 2002). The proteins encoded by these gene members form dimers that bind to the pseudopalindromic sequence CAAT (C/G)ATTG with a slight difference from subfamily I members, that the recognized nucleotide located in the center of the target site.

The HD-Zip II family comprises 10 members (*ATHB2/HAT4*, *ATHB4*, *HAT1–HAT3*, *HAT9*, *HAT14*, *HAT17*, and *HAT22*) that can be subdivided into 4 clades (α – δ). It was already known that, all the HD-Zip II γ and δ proteins contain an LxLxL type of ERF-associated amphiphilic repression (EAR) motif (Ciarbelli *et al.*, 2008; Kagale *et al.*, 2010) and some of them were reported to act as negative regulators in several processes (Steindler *et al.*, 1999; Ohgishi *et al.*, 2001; Sawa *et al.*, 2002; Turchi *et al.*, 2013). All the γ (*ATHB2*, *HAT1*, *HAT2*) and δ genes (*ATHB4*, *HAT3*) have been shown to be rapidly upregulated by Low R/FR light, and kinetics of this induction was drastically reversed by High R/FR light ratio, which suggests that *HAT1*, *HAT3* and *ATHB4*, as *ATHB2*, are regulated by the phytochrome(s) (Ciarbelli *et al.*, 2008, Harris *et al.*, 2011).

Another study described that progressive loss of *HAT3*, *ATHB4*, and *ATHB2* activity causes developmental defects from embryogenesis onwards in a white-light condition (Brandt *et al.*, 2012; Turchi *et al.*, 2013). Cotyledon development and number are visibly altered in *hat3athb4* double mutant lines and that existed even in greater extent, in *hat3athb4athb2* mutant embryos (Turchi *et al.*, 2013). More intriguingly, these defects are found to

correlate with changes in auxin distribution pattern and response (Turchi *et al.*, 2013).

HAHB-10, A sunflower Hd-Zip II gene exhibits a close resemblance to *ATHB-2* in terms of its response and adaptation to changes in variable light conditions. Over expression of *HAHB-10* in *Arabidopsis* gives rise to a range of phenotypic deviations, including dark cotyledons, planar leaves, reduced life cycle and accelerated flowering (Rueda *et al.*, 2005). It also responds towards biotic stress, mediated by phytohormones (Dezar *et al.*, 2011).

Previously, a HD-Zip II gene from *Capsicum*, *CaHB1*, has also been reported to participate in plant resistance against *Phytophthora infestans*, when overexpressed in tomato. Beside this, the expression of this gene also affects the leaf morphology and plant response to salt stress (Oh *et al.*, 2013). In rice also, three Class II transcripts, namely, *OsHOX11*, *OsHOX27* and *OsHOX19* behaves differentially in water deficit conditions, depending upon the rice cultivar and drought severity (Agalou *et al.*, 2008). These emerging findings strongly suggests an additional role of these genes in biotic and abiotic stress tolerance and plant development, apart from shade avoidance or light signalling.

Class III:

Members of Class III HD Zip Subfamily have been characterised by the presence of a Leucine zipper domain, a highly conserved lipid or sterol-binding START (Steroidogenic acute regulatory protein-related lipid transfer) domain followed by an adjacent conserved region called SAD (START-adjacent domain), the DNA-interacting PAS-related MEKHLA domain, and a homeodomain (Baima *et al.*, 1995, Mukherjee and Burglin, 2006). The binding domain of class III members has four additional amino acids between the HD and LZ domains. The HD-Zip III family constitutes of only 5 members, i.e. *REVOLUTA/ INTERFASCICULAR FIBERLESS1 (REV/IFL1)*, *PHABULOSA (PHB)*, *PHAVOLUTA (PHV)*, *CORONA (CAN/ AtHB15)* and *AtHB8* (Prigge *et al.*, 2005). The HD- TFs has been found to exhibit overlapping, antagonistic or distinct roles to regulate a number of developmental processes, such as embryogenesis with its patterning, meristem initiation and homeostasis, primary and secondary growth, determination of lateral organ polarity, auxin transport and vascular system development



in *Arabidopsis* (Baima *et al.*, 2001, McConnell *et al.*, 2001, Ochando *et al.*, 2006, Ochando *et al.*, 2008, Ohashi *et al.*, 2003, Ohashi *et al.*, 2005, Prigge *et al.*, 2005).

Arabidopsis revoluta (*rev*) plants are the unique single mutants among this subfamily which exhibit a distinct phenotype with an abnormality in shoot and leaves development, stem cell specification, vascular development and auxin transport (Otsuga *et al.*, 2001, Prigge *et al.*, 2005, Prigge *et al.*, 2006).

The mode of action of *REV*, *PHB* and *PHV* was thoroughly studied, together with *KANADI* in controlling abaxial-adaxial patterning of lateral organs (Emery *et al.*, 2003).

Arabidopsis PHB, *PHV* and *REV* often exhibit overlapping functions during embryogenesis and in the determination of leaf polarity (Ariel *et al.*, 2007). Generation of transgenic triple mutant lines of *phb phv rev* were shown to be associated with an aberrant amphicribal vasculature structure with xylem surrounded by phloem. On the other hand, gain-of-function mutations of any of these 3 genes, *PHB*, *PHV* or *REV*, have resulted in a complete opposite phenotype which is characterised by an amphivasal vasculatures with phloem surrounded by xylem (McConnell *et al.*, 1998, McConnell *et al.*, 2001, Zhong *et al.*, 2004).

All HD-Zip III genes are transcriptionally and posttranscriptionally regulated, specifically by two important miRNAs (*miR165* and *miR166*) (Emery *et al.*, 2003, Mallory *et al.*, 2004). In *jabba-1D* (*jba-1D*) plants, high abundance of these miRNAs down regulate the transcripts of three HD-Zip III genes: *PHABULOSA* (*PHB*), *PHAVOLUTA* (*PHV*) and *CORONA* (*CNA*), which leads to an expanded *WUS* expression domain, producing an enlarged SAM (Williams *et al.*, 2005). Overexpression of *miR166/165* promotes root growth by reducing the HD-Zip III transcripts in root, thereby enhancing the meristematic activity and cell division. This result depicts the importance of a balanced level of *miR166/165* and HD-Zip III transcripts in maintaining a proper root apical meristem (RAM) growth and activity in plants (Singh *et al.*, 2014).

Class IV:

HD-Zip IV TFs consist a large subfamily of genes, composed of 16 members (*GLABRA2/ ATHB10*,

ATML1, *ANL2*, *PDF2*, *HDG1–HDG5*, *HDG6/FWA* and *HDG7–HDG12*). This group of proteins has also been named HD-Zip GL2 based on *Arabidopsis* *GLABRA2* protein, which was identified first amongst the members (Nakamura *et al.*, 2006). The proteins encoded by these genes also have the domain organisation HD-Zip–START–SAD, alike of HD-Zip III, although their binding and dimerization features bear a closer resemblance to the subfamilies I and II (Schrik *et al.*, 2004). This family member can be distinguished from the others (I, II, III) by the presence of a loop in the middle of the LZ domain and absence of the MEKHLA motif. Majority of the HD-Zip IV proteins from *Arabidopsis* preferentially bind an 11 bp-long palindromic sequence 5'-GCATT(A/T)AATGC-3', which overlaps with the sequence of the L1 box (5'-TAAATG(C/T)A-3'), recognized in vitro by *ATML1* (Abe *et al.*, 2003).

Expression of all HD-Zip IV proteins are specifically restricted to the epidermal or subepidermal cell layer of the plant thus, these proteins are thought to be closely associated to trichome formation, anthocyanin accumulation, cuticle biosynthesis, and lipid transport (Abe *et al.*, 2003; Nadakuduti *et al.*, 2012).

In *Arabidopsis*, *Anthocyaninless2* (*ANL2*) affects the anthocyanin accumulation in epidermal and sub epidermal cell, mutation of which results in reduced accumulation. *HDG11* is another HD-Zip IV family member whose single mutants results in aberrant phenotype, i.e. trichomes with excess branching, whereas this phenotype become more severe in the *hdg11/12* double mutant (Nakamura *et al.*, 2006). On the other hand, overexpression of this gene imparts tolerance to drought in *Arabidopsis*, tobacco, sweet potato, rice, and cotton (Ruan *et al.*, 2012), indicating a novel function of this gene in abiotic stress. It also aids in yield increment in transgenic rice and cotton (Yu *et al.*, 2015). The *gl2* (*GLABRA2*) mutant revealed morphogenetic abnormality in trichome expansion and ectopic root hair differentiation (Cristina *et al.*, 1996). *HOMEODOMAIN GLABROUS2* (*HDG2*) is found to highly accumulated in the meristem and promotes stomatal development (Peterson *et al.*, 2013). It is also reported that these HD-Zip IV genes have redundant function. For instance, *GL2* and *HDG11* act redundantly in *Arabidopsis* trichome development (Khosla *et al.*, 2014). *AMTL1* and *PDF2*



exhibit redundant functions in shoot epidermal cell differentiation and embryo development. Double mutants of these genes render the plants defective in epidermis formation and the plants fail to survive (Abe *et al.*, 2003, Ogawa *et al.*, 2015).

OCL1 (OUTER CELL LAYER1) encodes a maize HD-Zip class IV gene, which have been reported to have a pivotal role in regulating several genes involved in lipid metabolism and cuticle biosynthesis (Javelle *et al.*, 2010). Functional analysis of another member of this group, *OCL4 (OUTER CELL LAYER4)* has revealed that it inhibits trichome development and influences anther cell wall morphogenesis (Vernoud *et al.*, 2009). Two functional homologs of *GL2*, *GaHOX1* and *GbML* participate in cotton fiber formation (Zhang *et al.*, 2010). Gao *et al.*, (2015) have recently found that most of HD-Zip IV genes in tomato can be induced by at least one abiotic stress or they respond to one or more phytohormones, thereby suggesting their potential functions in such processes.

Conclusion and Future Perspectives

Substantial progresses in various functional aspects of HD-Zip transcription factors have been obtained over the past few years. HD-Zip proteins participate in diverse and often overlapping events ranging from stress responses to morphogenesis, development and responses to light and hormones. Functional analyses have revealed that they function by invoking the activation of downstream target genes related to various pathways that ultimately leads to better plant adaptation to surroundings.

Therefore, these proteins can be used as a potential candidate for plant breeding. Nevertheless, many missing links still remain there. In order to achieve a better understanding of their role during multiple physiological events, it is of great importance to identify the interacting partner of HD-Zip proteins under a given situation which may cooperate in regulating the transcription of downstream target genes. This is also important to determine the key components of signal transduction network during stress adaptation with which they interact, directly or indirectly. So, it can be expected that further molecular studies of HD-Zip transcription factors will certainly help to elucidate the complex mechanisms of signalling and transcriptional reprogramming under multiple stresses as well

as developmental phases, which are controlled by HD-Zip proteins in plants. Moreover, the substantial knowledge of a complete and fine tuned stress tolerance mechanism will definitely add significant benefits to a better agricultural productivity.

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