



# A Review of Auxin Response Factors (ARFs) in Plants

Si-Bei Li <sup>†</sup>, Zong-Zhou Xie <sup>†</sup>, Chun-Gen Hu and Jin-Zhi Zhang <sup>\*</sup>

Key Laboratory of Horticultural Plant Biology, Ministry of Education, College of Horticulture and Forestry Science, Huazhong Agricultural University, Wuhan, China

## OPEN ACCESS

### Edited by:

Elena Prats,  
Consejo Superior de Investigaciones  
Científicas, Spain

### Reviewed by:

Lei Zhang,  
Washington State University, USA  
Caiguo Zhang,  
University of Colorado, Denver, USA

### \*Correspondence:



**Jin-Zhi Zhang**

Dr. Zhang engaged in research work at the Institute for Huazhong Agricultural University, China. He holds a Master and Ph.D. from Huazhong Agricultural University in the area of fruit molecular biology. After receiving his Ph.D., He worked as a visiting scholar investigates auxin biosynthesis and its regulation in the section of cell and developmental biology at University of California at San Diego. Zhang's work utilizes an early-flowering mutant of citrus as a model system to investigate the developmental genetic mechanisms that control how flowers are formed and elaborated in past year. Now, he is also engaged in understanding the transcriptional mechanisms and signaling processes that control fruit development.  
jinzhizhang@mail.hzau.edu.cn;  
jinzhi327320094@126.com

<sup>†</sup>These authors have contributed equally to this work.

**Received:** 04 November 2015

**Accepted:** 12 January 2016

**Published:** 03 February 2016

### Citation:

Li S-B, Xie Z-Z, Hu C-G and Zhang J-Z (2016) A Review of Auxin Response Factors (ARFs) in Plants. *Front. Plant Sci.* 7:47. doi: 10.3389/fpls.2016.00047

Auxin is a key regulator of virtually every aspect of plant growth and development from embryogenesis to senescence. Previous studies have indicated that auxin regulates these processes by controlling gene expression via a family of functionally distinct DNA-binding *auxin response factors (ARFs)*. *ARFs* are likely components that confer specificity to auxin response through selection of target genes as transcription factors. They bind to auxin response DNA elements (AuxRE) in the promoters of auxin-regulated genes and either activate or repress transcription of these genes depending on a specific domain in the middle of the protein. Genetic studies have implicated various *ARFs* in distinct developmental processes through loss-of-function mutant analysis. Recent advances have provided information on the regulation of *ARF* gene expression, the role of *ARFs* in growth and developmental processes, protein-protein interactions of *ARFs* and target genes regulated by *ARFs* in plants. In particular, protein interaction and structural studies of *ARF* proteins have yielded novel insights into the molecular basis of auxin-regulated transcription. These results provide the foundation for predicting the contributions of *ARF* genes to the biology of other plants.

**Keywords:** auxin, *ARF*, auxin response DNA elements, *Arabidopsis*, DBD domain, a type I/II Phox and Bem1p (PB1)

## INTRODUCTION

Auxins play a critical role in most major growth responses both throughout the different developmental stages of plants such as **organogenesis**, vascular tissue differentiation, apical dominance and root initiation, and tropism and on a cellular level cell in processes including extension, division, and differentiation (Guilfoyle and Hagen, 2007; Mockaitis and Estelle, 2008; Su et al., 2014). Three decades of studies have explored the rapid effects of auxin on gene expression and regulation (Di et al., 2015b). A large number of candidate genes that are potentially regulated by auxins and that may function in growth and developmental processes have been identified in *Arabidopsis* and other plant species (Rosado et al., 2012; Liu et al., 2014b; Di et al., 2015b; Guilfoyle, 2015). Among these genes, members of the *auxin response factors (ARF)* family have been suggested to play a key role in regulating the expression of auxin response genes (Liscum and Reed, 2002). To date, 22 *ARF* genes and one pseudogene have been isolated from *Arabidopsis* (Liscum and Reed, 2002; Guilfoyle and Hagen, 2007). *ARF* genes are expressed in dynamic and differential patterning during development, and genetic studies have shown that individual *ARFs* control distinct developmental processes (Rademacher et al., 2012). Members of the *ARF* family of proteins contain domains associated with DNA binding, transcriptional activation or repression, and protein-protein interactions during auxin perception and signaling processes (Guilfoyle and Hagen, 2007; Di et al., 2015a). Recently, the *ARF* gene family has been also investigated in several plants based on the recent release of the genome such as citrus, *Medicago truncatula* and *Gossypium*

**KEY CONCEPT 1 | Organogenesis**

An adult plant consists of many specialized cell organizations: tissues and organs. Tissues consist of cells of uniform shape and specialized function, such as meristem, cortex, and phloem. Several tissues are organized together to form an organ, such as leaves, roots, flowers, and fruit. The process of initiation and development of an organ is called organogenesis.

*raimondii* using both bioinformatics and molecular analyses (Li et al., 2015; Shen et al., 2015a; Sun et al., 2015). More importantly, a considerable amount of new information has been obtained regarding the mechanisms that control ARF protein activities, and gene expression profiles. This review will focus on recent advances that have provided insight into the roles played by ARFs in regulating a variety of plant growth and development processes and the mechanisms involved in this regulation in *Arabidopsis* and other plant species.

## MOLECULAR STRUCTURE OF ARF FAMILY PROTEINS

The plants response to auxin involves changes in gene regulation (Liscum and Reed, 2002). Genes that are up-regulated or down-regulated by auxin contain AuxRE in their promoters, which bind transcription factors of the ARF family (Guilfoyle and Hagen, 2007; Mockaitis and Estelle, 2008). The identification of the AuxRE sequence led to the isolation of *Arabidopsis* ARF1 (Ulmasov et al., 1997), and subsequent genetic, genomic, and molecular studies have identified 22 ARF genes in *Arabidopsis* (Liscum and Reed, 2002). The ARF gene family is a modular transcription factor family consisting of several domains that have remained conserved despite hundreds of millions of years of evolution (Finet et al., 2012). Most ARF proteins consist of an N-terminal **B3-type DNA binding domain (DBD)**, a variable middle region that functions as an activation domain (AD) or repression domain (RD), and a carboxy-terminal dimerization domain (CTD: domain III/IV), which is involved in protein-protein interactions by dimerizing with auxin/indole-3-acetic acid (Aux/IAA) family genes as well as between ARFs (Kim et al., 1997; Guilfoyle and Hagen, 2007; Piya et al., 2014). The DBD is classified as a plant-specific B3-type protein domain, but requires additional amino-terminal and carboxyterminal amino acids for efficient *in vitro* binding to TGTCTC/GAGACA site (Tiwari et al., 2003). The first four bases of the recognition site are absolutely required for ARF binding, while more variation is tolerated in the last two bases (Boer et al., 2014). The AD and RD are located just carboxyterminal to the DBD and contain biased amino acid sequences (Ulmasov et al., 1999). The AD is enriched in glutamine along with leucine (L) and serine (S) residues, while the RD is enriched in glycine (Q), leucine (L), serine (S), and proline (P) residues (Ulmasov et al., 1999). The amino acid composition of the middle region is critical in determining ARF function, with S-rich ARFs acting as transcriptional repressors and Q-rich ARFs acting transcriptional activators by protoplast transfection assays (Tiwari et al., 2003; Guilfoyle and Hagen, 2007). Five ARF

proteins (ARF5/ARF6/ARF7/ARF8/ARF19) were characterized as transcriptional activators based on transient assays in transfected protoplasts, the other ARFs were classified as repressors (Ulmasov et al., 1999; Tiwari et al., 2003). A recent crystallographic study revealed that two additional domains associate with the DBDs of some ARFs, and these are a dimerization domain (DD) and a Tudor-like ancillary domain within the C-terminal region of the flanking domain (FD). The DD facilitates cooperative binding of the B3 DBD to selected AuxREs. However, the function of Tudor-like ancillary domain has not been determined (Guilfoyle and Hagen, 2012; Boer et al., 2014; Guilfoyle, 2015; Korasick et al., 2015). Not all ARFs contain the five domains described above. In addition, the III-IV region of some ARF protein may form a type I/II Phox and Bem1p (PB1) protein-protein interaction domain, which provides both positive and negative electrostatic interfaces for directional protein interaction (Guilfoyle and Hagen, 2012; Guilfoyle, 2015; Korasick et al., 2015).

**KEY CONCEPT 2 | B3-type DNA binding domain (DBD)**

It is a highly conserved domain found exclusively in transcription factors (TFs) of higher plants. It consists of 100–120 residues, includes seven beta strands and two alpha helices. There are three main families of TFs that contain B3 domain in *Arabidopsis*: ARF Auxin response factors (ARF), Abscisic acid insensitive 3 (ABI3), and Related to ABI3/VP1 (RAV).

Since, cloning of the first ARF gene from *Arabidopsis* (Ulmasov et al., 1997), ARF genes from 15 plant species have been identified based on genome-wide analysis studies (Table 1). For example, 22 genes from tomato (Zouine et al., 2014), 25 genes from rice (Wang et al., 2007), 19 genes from sweet orange (Li et al., 2015), 24 genes from *Medicago truncatula* (Shen et al., 2015a), 47 genes from banana (Hu et al., 2015), and 39 genes from *Populus trichocarpa* (Kalluri et al., 2007) were identified. Most ARF proteins from these plant species are nuclear proteins with described protein domains consistent with previous reports on the homologous genes from *Arabidopsis* (Table 1). However, some differences in the ARF protein family were also found between *Arabidopsis* and other plant species. For example, ARF3, ARF13, and ARF17 lack Domains III/IV, and ARF23 consists of a truncated DBD only in *Arabidopsis* (Guilfoyle and Hagen, 2007). Only one pseudogene (a truncated DBD) was found in citrus plants among these plant species (Li et al., 2015), whereas a large number of truncated proteins (lacking Domains III/IV) have been found in rice (Wang et al., 2007), maize (Liu et al., 2011), banana (Hu et al., 2015), and *M. truncatula* (Shen et al., 2015a) compared with *Arabidopsis*. Interestingly, some plant species contain more ARF genes than *Arabidopsis* (Table 1). One explanation for the higher number of ARF genes encoded in these genome could be that large-scale duplication event occurred early in the evolution of these plants (Blanc et al., 2003). It is noteworthy that most information about ARFs function, expression, and regulation comes from studies in annual herbaceous plants such as *Arabidopsis*, rice, and tomato (Guilfoyle and Hagen, 2007; Wang et al., 2007; Kumar et al., 2011), while relatively few reports focus on other plant species.

**TABLE 1 | Summary of ARF genes in 16 plant species based on genome-wide analysis.**

Species	Gene No	Pseudogene No	Truncated protein No.	Complete protein No.	References
<i>Arabidopsis thaliana</i>	23	1	3 (DBD, MR)	19 (DBD, MR, CTD)	Hagen and Guilfoyle, 2002
<i>Oryza sativa</i>	25	0	6 (DBD, MR)	19 (DBD, MR, CTD)	Wang et al., 2007
<i>Citrus sinensis</i>	19	1	3 (DBD, MR)	15 (DBD, MR, CTD)	Li et al., 2015
<i>Solanum lycopersicum</i>	21	0	7 (DBD, MR)	14 (DBD, MR, CTD)	Wu et al., 2011
<i>Glycine max</i>	51	0	8 (DBD, MR)	43 (DBD, MR, CTD)	Van Ha et al., 2013
<i>Zea mays</i>	36	0	11 (DBD, MR)	25 (DBD, MR, CTD)	Liu et al., 2011
<i>Populus trichocarpa</i>	39	0	0	35 (DBD, MR, CTD)	Kalluri et al., 2007
Banana	47	0	12 (DBD, MR)	35 (DBD, MR, CTD)	Hu et al., 2015
<i>Brassica rapa</i>	31	0	4 (DBD, MR)	27 (DBD, MR, CTD)	Mun et al., 2012
<i>Vitis vinifera</i>	19	0	2 (DBD, MR)	17 (DBD, MR, CTD)	Wan et al., 2014
<i>Medicago truncatula</i>	24	0	14 (DBD, MR)	10 (DBD, MR, CTD)	Shen et al., 2015a
<i>Gossypium raimondii</i>	35	0	7 (DBD, MR)	28 (DBD, MR, CTD)	Sun et al., 2015
<i>Cucumis sativus</i>	15	0	1 (DBD, MR)	14 (DBD, MR, CTD)	Liu and Hu, 2013
<i>Eucalyptus grandis</i>	17	0	3 (DBD, MR)	14 (DBD, MR, CTD)	Yu et al., 2014
<i>Malus domestica</i>	31	0	8 (DBD, MR)	23 (DBD, MR, CTD)	Luo et al., 2014
<i>Carica papaya L.</i>	11	0	3 (DBD, MR)	7 (DBD, MR, CTD)	Liu et al., 2015

## ACTIVATION, INTERACTION, AND REGULATORY MECHANISMS OF ARFs IN PLANTS

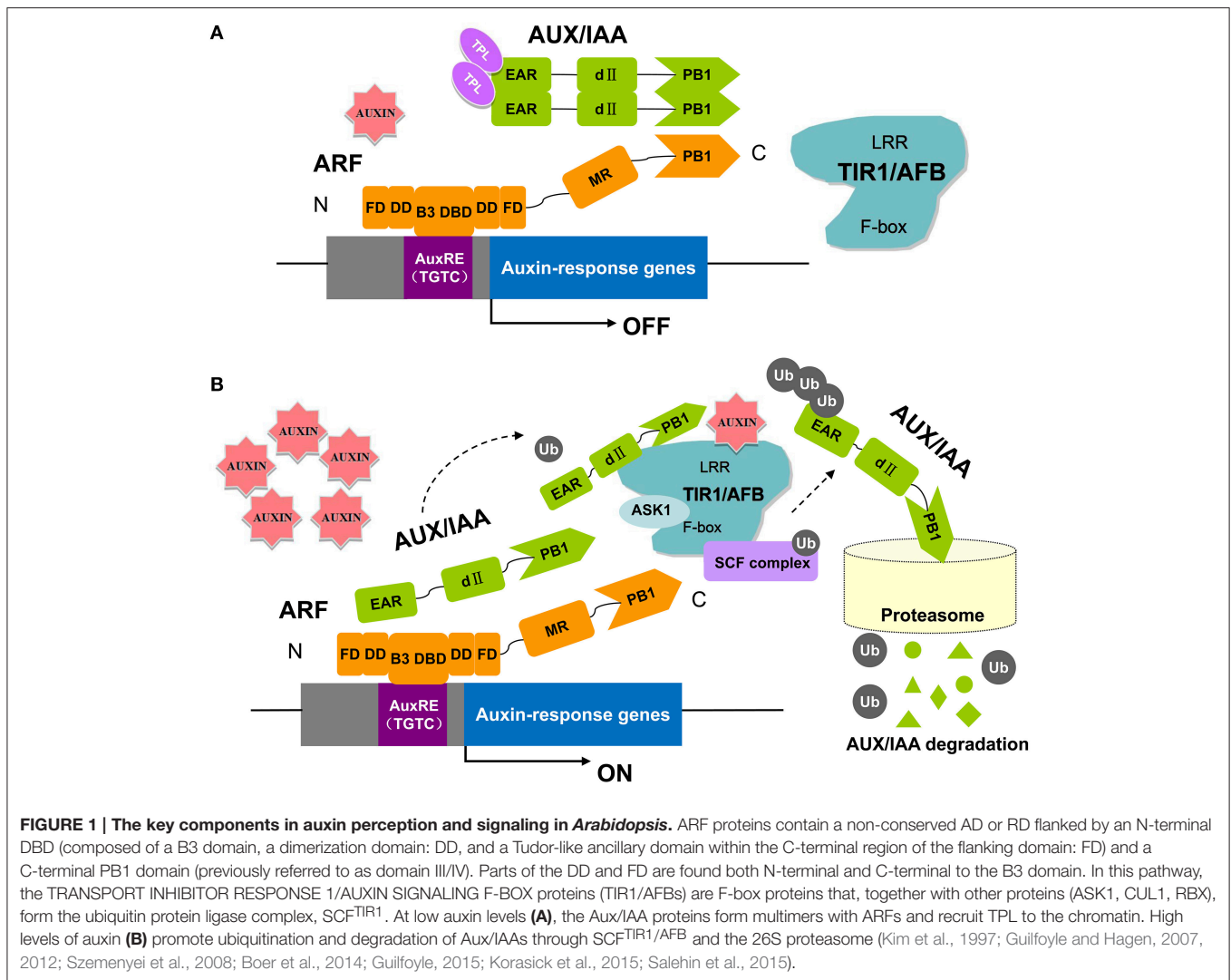
The ARF genes encode proteins with full-length DBDs that may recognize and compete for target sites in promoters of auxin response genes (Tiwari et al., 2003). Therefore, there has been increased interest to determining when and where these genes are expressed and what regulates their expression (Hagen and Guilfoyle, 2002; Guilfoyle and Hagen, 2007). It has long been recognized that ARFs directly bind to AuxREs in the promoters of auxin responsive genes through their DNA-binding domain (Wang and Estelle, 2014). ARF binding to AuxREs in particular requires C-terminal amino acids (Guilfoyle and Hagen, 2012). It has been proposed that the C-terminal domain enhances DNA binding by enabling ARF dimerization. Both ARF and Aux/IAA proteins contain conserved sequences near the C-terminus termed domains III and IV (Guilfoyle and Hagen, 2012). These domains mediate ARF-ARF, ARF-Aux/IAA, and Aux/IAA-Aux/IAA interactions as determined by yeast two-hybrid and **bimolecular fluorescence complementation assays** (Korasick et al., 2015). ARF regulation is well-studied, and a working model for ARF activation is now well-established (**Figure 1**) (Salehin et al., 2015). At low auxin levels, Aux/IAA proteins form dimers with ARFs to inhibit ARF activity by recruiting the co-repressor TOPLESS (TPL), which results in the repression of auxin-responsive genes (**Figure 1A**) (Szemenyei et al., 2008). At higher auxin levels, Aux/IAAs bind to the SCF<sup>TIR1/AFB</sup> complex and subsequently become ubiquitinated and degraded by the 26S proteasome. The ARF is then released and can regulate the transcription of its target auxin response genes (**Figure 1B**) (Wang and Estelle, 2014). Recent structural studies of ARFs have led to exciting new insight into the molecular function of the ARF-Aux/IAA pathway. Crystal structures showed that the C-terminal domains of ARF5 and ARF7

conform to a well-known PB1 domain that confers protein-protein interactions with other PB1 domain proteins through electrostatic contacts (Boer et al., 2014; Guilfoyle, 2015). Further experiments confirmed the importance of these charged amino acids in conferring ARF and Aux/IAA interactions as proposed by the crystal structure of the PB1 domain (Korasick et al., 2015). In addition to the PB1 domain, a second protein-protein interaction module that functions in ARF-ARF dimerization and facilitates DNA binding has recently been revealed from structure-function analysis and saturating binding site selection on the ARF1 and ARF5 DNA binding domains (Boer et al., 2014). These studies provide an atomic-level explanation for DNA-binding specificity in the auxin pathway.

### KEY CONCEPT 3 | Bimolecular fluorescence complementation assays

It is a technology typically used to validate protein interactions. It is based on the association of fluorescent protein fragments that are attached to components of the same macromolecular complex. Through the visualization and analysis of the intensity and distribution of fluorescence in live cells, one can identify both the location and interaction partners of proteins of interest.

In addition to the interaction between themselves, the ARFs have also been reported to regulate and be regulated by other transcription factors (Wang and Estelle, 2014). A recent study showed that a MYB transcription factor (*MYB77*) interacts with the ARF7 protein and that this interaction results in a strong reduction in lateral root numbers in *Arabidopsis* (Shin et al., 2007). Moreover, it has been shown that the bHLH transcription factor BIGPETALp (BPEp) interacts with ARF8 to effect petal growth. This interaction is mediated through the BPEp C-terminal domain and the C-terminal domain of ARF8 (Varaud et al., 2011). The *Arabidopsis* BREVIS RADIX (BRX) transcriptional co-regulator interacts with domain III/IV of ARF5 in yeast two-hybrid assays as well as *in vitro* pull-down assays, and this interaction enhances the transcriptional activation potential of this ARF (Guilfoyle and Hagen, 2012).



In another recent report, HaIAA27 was shown to repress the transcriptional activation of the heat shock transcription factor HaHSFA9 in sunflower to repress its activity during seed development. As in the case of the ARFs, auxin also acts to relieve repression of the HaHSFA9 protein (Carranco et al., 2010). Recent data also suggest that post-translational modifications of ARFs may constitute another layer of regulation of auxin signaling outputs (Wang and Estelle, 2014; Hill, 2015). Phosphorylation of ARF7 and ARF19 by BRASSINOSTEROID-INSENSITIVE2 (BIN2) can potentiate auxin signaling output during lateral root organogenesis (Cho et al., 2014). Meanwhile, other previous report shows that BIN2 also phosphorylates ARF2 (Vert et al., 2008). These data suggest that ARF phosphorylation suppresses their interaction with Aux/IAs, thus enhancing DNA binding and transcriptional activity. In addition, there is a growing body of evidence on the posttranscriptional regulation of ARF transcript abundance by miRNA and **transacting-small interfering RNAs (ta-siRNA)**. While *ARF6* and *ARF8* are targets of miR167 and *ARF10*, *ARF16*, and *ARF17* are targeted by

miR160, *ARF2*, *ARF3*, and *ARF4* are targets of TAS3 ta-siRNAs in *Arabidopsis* (Rhoades et al., 2002; Williams et al., 2005; Guilfoyle and Hagen, 2007; Lin et al., 2015).

#### KEY CONCEPT 4 | Transacting-small interfering RNAs (Ta-siRNAs)

Ta-siRNAs are form of small interfering RNA (siRNA) that represses gene expression through post-transcriptional gene silencing in land plants. They are transcribed from the genome to form a polyadenylated, double-stranded segment of RNA that gets processed further, resulting in a segment of RNA that is 21-nucleotides long. These segments are incorporated into the RNA-induced Silencing Complex and direct the cleavage of target mRNA.

## ROLES OF ARFs IN PLANT GROWTH AND DEVELOPMENTAL PROCESSES

The *Arabidopsis* genome encodes 23 ARF proteins (Rademacher et al., 2011) and genetic analyses have shown that individual ARFs control distinct developmental processes based on their loss-of-function mutant phenotypes (Guilfoyle and Hagen, 2007;

Rademacher et al., 2012). Although ARFs appear to have unique functions in some contexts, they display overlapping functions in others. For example, both *ARF1* and *ARF2* control leaf senescence and floral organ abscission in *Arabidopsis* (Ellis et al., 2005), while *ARF3* interacts with KANADI proteins to form a functional complex essential for leaf polarity specification (Kelley et al., 2012). A recent study indicated that *ARF3* integrates the functions of *AGAMOUS* (*AG*) and *APETALA2* (*AP2*) in floral meristem determinacy (Liu et al., 2014b), while *ARF4* has been studied primarily for its role in organ polarity (Hunter et al., 2006). However, the *arf3arf4* double mutant plant has reduced abaxial identity in all lateral organs, including leaves (Pekker et al., 2005; Finet et al., 2010). *ARF5* is critically required for embryonic root and flower formation (Hardtke and Berleth, 1998) and embryo patterning and vasculature defects observed in *arf5* mutants are enhanced in *arf5arf7* double mutants (Hardtke and Berleth, 1998). *ARF8* is reported to regulate fertilization and fruit development (Goetz et al., 2006), and *ARF6* and *ARF8* act redundantly in flower maturation (Finet et al., 2010). *ARF19* and *ARF7* act redundantly with in controlling leaf expansion and lateral root growth (Wilmoth et al., 2005). While no phenotypic defects were reported for *arf10* or *arf16* single mutants (Okushima et al., 2005), *arf10arf16* double mutants show a strong auxin phenotype that results in the absence of lateral root formation, which is not observed in neither the *arf10* or *arf16* single mutant (Wang et al., 2005).

In the case of tomato, genetic studies have shown that the mechanism of *ARF* signaling is different to that of *Arabidopsis*. A total of 21 putative functional *SlARFs* have been identified in tomato (Zouine et al., 2014). Although, *SlARF3* RNAi lines do not display phenotypes such as floral organogenesis or developmental timing changes (Sessions et al., 1997), *SlARF3* plays multiple roles in tomato development and is involved in the formation of epidermal cells and trichomes (Zhang et al., 2015b). The functional analysis of *SlARF9* indicated that it regulates cell division during early tomato fruit development (DeJong et al., 2015). A recent study confirmed that down-regulation of *ARF6* and *ARF8* by mi167 leads to floral development defects and female sterility in tomatoes. These results indicate that *ARF6* and *ARF8* have conserved roles in controlling growth and development of vegetative and flower organs in dicots (Liu et al., 2014a). *SlARF7* acts as a negative regulator of fruit set until pollination and fertilization have taken place and moderates the auxin response during fruit growth in tomatoes (de Jong et al., 2009). Meanwhile, *SlARF7* mediates cross-talk between auxin and gibberellin signaling during tomato fruit set and

development (de Jong et al., 2011). Interestingly, *SlARF4* is involved in the control of sugar metabolism during tomato fruit development (Sagar et al., 2013). In soybeans, the miR167-directed regulation of *GmARF8a* and *GmARF8b* is required for nodulation and lateral root development (Wang et al., 2015). In rice, *OsARF16* and *OsARF12* are required for iron deficiency response by regulating auxin redistribution (Wang et al., 2014; Shen et al., 2015b). *OsARF3* mediates the auxin response during de novo shoot regeneration (Cheng et al., 2013). *OsARF19* controls rice leaf angles through positively regulating *OsGH3-5* and *brassinosteroid insensitive 1* (*OsBRI1*) in rice (Zhang et al., 2015a).

## CONCLUSION AND PERSPECTIVES

During the last 10 years, our understanding of *ARF* regulatory mechanism and their role during model plant growth and development has been greatly improved by forward and reverse genetic approaches. Nonetheless, there are still many gaps in our knowledge and we lack a deep understanding of these regulatory processes. For example, it is still not clear how repressors of *ARFs* regulate gene repression and how other transcription factors and signaling proteins interact with *ARF* proteins. However, a larger number of candidate genes that are regulated by *ARFs* have been identified both experimentally and through bioinformatics analysis in recent years. Therefore, it will be interesting to understand the function of these candidate genes and regulatory mechanism of some important *ARF* proteins. In addition, our knowledge of *ARFs* in plant species beyond model plants (typically *Arabidopsis*) is very limited. The great challenge will be to integrate knowledge about *ARF* regulation of different developmental processes across in plants, and to understand how these processes work in different plant species.

## AUTHOR CONTRIBUTIONS

JZ, SL, and ZX wrote the paper. CH provided some suggestions for the paper.

## ACKNOWLEDGMENTS

This research was supported financially by the National Natural Science Foundation of China (grant nos. 31130046, 31471863, 31360469, and 31372046), the Fundamental Research Funds for the Central Universities (2013PY083) and the International Foundation for Science No. C/5148-2.

## REFERENCES

- Blanc, G., Hokamp, K., and Wolfe, K. H. (2003). A recent polyploidy superimposed on older large-scale duplications in the *Arabidopsis* genome. *Genome Res.* 13, 137–144. doi: 10.1101/gr.751803
- Boer, D. R., Freire-Rios, A., van den Berg, W. A., Saaki, T., Manfield, I. W., Kepinski, S., et al. (2014). Structural basis for DNA binding specificity by the auxin-dependent *ARF* transcription factors. *Cell* 156, 577–589. doi: 10.1016/j.cell.2013.12.027
- Carranco, R., Espinosa, J. M., Prieto-Dapena, P., Almoguera, C., and Jordano, J. (2010). Repression by an auxin/indole acetic acid protein connects auxin signaling with heat shock factor-mediated seed longevity. *Proc. Natl. Acad. Sci. U.S.A.* 107, 21908–21913. doi: 10.1073/pnas.1014856107
- Cheng, Z. J., Wang, L., Sun, W., Zhang, Y., Zhou, C., Su, Y. H., et al. (2013). Pattern of auxin and cytokinin responses for shoot meristem induction results from the regulation of cytokinin biosynthesis by AUXIN RESPONSE FACTOR3. *Plant Physiol.* 161, 240–251. doi: 10.1104/pp.112.203166

- Cho, H., Ryu, H., Rho, S., Hill, K., Smith, S., Audenaert, D., et al. (2014). A secreted peptide acts on BIN2-mediated phosphorylation of ARFs to potentiate auxin response during lateral root development. *Nat. Cell Biol.* 16, 66–76. doi: 10.1038/ncb2893
- de Jong, M., Wolters-Arts, M., Feron, R., Mariani, C., and Vriezen, W. H. (2009). The *Solanum lycopersicum* auxin response factor 7 (SlARF7) regulates auxin signaling during tomato fruit set and development. *Plant J.* 57, 160–170. doi: 10.1111/j.1365-313X.2008.03671.x
- de Jong, M., Wolters-Arts, M., García-Martínez, J. L., Mariani, C., and Vriezen, W. H. (2011). The *Solanum lycopersicum* AUXIN RESPONSE FACTOR 7 (SlARF7) mediates cross-talk between auxin and gibberellin signalling during tomato fruit set and development. *J. Exp. Bot.* 62, 617–626. doi: 10.1093/jxb/erq293
- DeJong, M., Wolters-Arts, M., Schimmel, B. C., Stultiens, C. L., de Groot, P. F., Powers, S. J., et al. (2015). *Solanum lycopersicum* AUXIN RESPONSE FACTOR 9 regulates cell division activity during early tomato fruit development. *J. Exp. Bot.* 66, 3405–3416. doi: 10.1093/jxb/erv152
- Di, D.-W., Zhang, C., and Guo, G.-Q. (2015a). Involvement of secondary messengers and small organic molecules in auxin perception and signaling. *Plant Cell Rep.* 34, 895–904. doi: 10.1007/s00299-015-1767-z
- Di, D.-W., Zhang, C., Luo, P., An, C.-W., and Guo, G.-Q. (2015b). The biosynthesis of auxin: how many paths truly lead to IAA? *Plant Growth Regul.* 1–11. doi: 10.1007/s10725-015-0103-5. [Epub ahead of print].
- Ellis, C. M., Nagpal, P., Young, J. C., Hagen, G., Guilfoyle, T. J., and Reed, J. W. (2005). AUXIN RESPONSE FACTOR1 and AUXIN RESPONSE FACTOR2 regulate senescence and floral organ abscission in *Arabidopsis thaliana*. *Development* 132, 4563–4574. doi: 10.1242/dev.02012
- Finet, C., Berne-Dedieu, A., Scutt, C. P., and Marlétaz, F. (2012). Evolution of the ARF gene family in land plants: old domains, new tricks. *Mol. Biol. Evol.* 30, 45–56. doi: 10.1093/molbev/mss220
- Finet, C., Fourquin, C., Vinauger, M., Berne-Dedieu, A., Chambrier, P., Paindavoine, S., et al. (2010). Parallel structural evolution of auxin response factors in the angiosperms. *Plant J.* 63, 952–959. doi: 10.1111/j.1365-313X.2010.04292.x
- Goetz, M., Vivian-Smith, A., Johnson, S. D., and Koltunow, A. M. (2006). AUXIN RESPONSE FACTOR8 is a negative regulator of fruit initiation in *Arabidopsis*. *Plant Cell* 18, 1873–1886. doi: 10.1105/tpc.105.037192
- Guilfoyle, T. J. (2015). The PB1 domain in auxin response factor and Aux/IAA proteins: a versatile protein interaction module in the auxin response. *Plant Cell* 27, 33–43. doi: 10.1105/tpc.114.132753
- Guilfoyle, T. J., and Hagen, G. (2007). Auxin response factors. *Curr. Opin. Plant Biol.* 10, 453–460. doi: 10.1016/j.pbi.2007.08.014
- Guilfoyle, T. J., and Hagen, G. (2012). Getting a grasp on domain III/IV responsible for Auxin Response Factor–IAA protein interactions. *Plant Sci.* 190, 82–88. doi: 10.1016/j.plantsci.2012.04.003
- Hagen, G., and Guilfoyle, T. (2002). Auxin-responsive gene expression: genes, promoters and regulatory factors. *Plant Mol. Biol.* 49, 373–385. doi: 10.1023/A:1015207114117
- Hardtke, C. S., and Berleth, T. (1998). The *Arabidopsis* gene MONOPTEROS encodes a transcription factor mediating embryo axis formation and vascular development. *EMBO J.* 17, 1405–1411. doi: 10.1093/emboj/17.5.1405
- Hill, K. (2015). Post-translational modifications of hormone-responsive transcription factors: the next level of regulation. *J. Exp. Bot.* 66, 4933–4945. doi: 10.1093/jxb/erv273
- Hu, W., Zuo, J., Hou, X., Yan, Y., Wei, Y., Liu, J., et al. (2015). The auxin response factor gene family in banana: genome-wide identification and expression analyses during development, ripening, and abiotic stress. *Front. Plant Sci.* 6:742. doi: 10.3389/fpls.2015.00742
- Hunter, C., Willmann, M. R., Wu, G., Yoshikawa, M., de la Luz Gutiérrez-Nava, M., and Poethig, S. R. (2006). Trans-acting siRNA-mediated repression of *ETTIN* and *ARF4* regulates heteroblasty in *Arabidopsis*. *Development* 133, 2973–2981. doi: 10.1242/dev.02491
- Kalluri, U. C., Difazio, S. P., Brunner, A. M., and Tuskan, G. A. (2007). Genome-wide analysis of Aux/IAA and ARF gene families in *Populus trichocarpa*. *BMC Plant Biol.* 7:59. doi: 10.1186/1471-2229-7-59
- Kelley, D. R., Arreola, A., Gallagher, T. L., and Gasser, C. S. (2012). *ETTIN* (ARF3) physically interacts with KANADI proteins to form a functional complex essential for integument development and polarity determination in *Arabidopsis*. *Development* 139, 1105–1109. doi: 10.1242/dev.067918
- Kim, J., Harter, K., and Theologis, A. (1997). Protein–protein interactions among the Aux/IAA proteins. *Proc. Natl. Acad. Sci. U.S.A.* 94, 11786–11791. doi: 10.1073/pnas.94.22.11786
- Korasick, D. A., Chatterjee, S., Tonelli, M., Dashti, H., Lee, S. G., Westfall, C. S., et al. (2015). Defining a two-pronged structural model for PB1 (Phox/Bem1p) domain interaction in plant auxin responses. *J. Biol. Chem.* 290, 12868–12878. doi: 10.1074/jbc.M115.648253
- Kumar, R., Tyagi, A. K., and Sharma, A. K. (2011). Genome-wide analysis of auxin response factor (ARF) gene family from tomato and analysis of their role in flower and fruit development. *Mol. Genet. Genomics* 285, 245–260. doi: 10.1007/s00438-011-0602-7
- Li, S.-B., OuYang, W.-Z., Hou, X.-J., Xie, L.-L., Hu, C.-G., and Zhang, J.-Z. (2015). Genome-wide identification, isolation and expression analysis of auxin response factor (ARF) gene family in sweet orange (*Citrus sinensis*). *Front. Plant Sci.* 6:119. doi: 10.3389/fpls.2015.00119
- Lin, Y., Lai, Z., Tian, Q., Lin, L., Lai, R., Yang, M., et al. (2015). Endogenous target mimics down-regulate miR160 mediation of ARF10, -16 and -17 cleavage during somatic embryogenesis in *Dimocarpus longan* Lour. *Front. Plant Sci.* 6:956. doi: 10.3389/fpls.2015.00956
- Liscum, E., and Reed, J. (2002). Genetics of Aux/IAA and ARF action in plant growth and development. *Plant Mol. Biol.* 49, 387–400. doi: 10.1023/A:1015255030047
- Liu, K., Yuan, C., Li, H., Lin, W., Yang, Y., Shen, C., et al. (2015). Genome-wide identification and characterization of auxin response factor (ARF) family genes related to flower and fruit development in papaya (*Carica papaya* L.). *BMC Genomics* 16:901. doi: 10.1186/s12864-015-2182-0
- Liu, N., Wu, S., Van Houten, J., Wang, Y., Ding, B., Fei, Z., et al. (2014a). Down-regulation of AUXIN RESPONSE FACTORS 6 and 8 by microRNA 167 leads to floral development defects and female sterility in tomato. *J. Exp. Bot.* 65, 2507–2520. doi: 10.1093/jxb/eru141
- Liu, S. Q., and Hu, L. H. (2013). Genome-wide analysis of the auxin response factor gene family in cucumber. *Genet. Mol. Res.* 12, 4317–4331. doi: 10.4238/2013.April.2.1
- Liu, X., Dinh, T. T., Li, D., Shi, B., Li, Y., Cao, X., et al. (2014b). AUXIN RESPONSE FACTOR 3 integrates the functions of AGAMOUS and APETALA2 in floral meristem determinacy. *Plant J.* 80, 629–641. doi: 10.1111/tpl.12658
- Liu, Y., Jiang, H., Chen, W., Qian, Y., Ma, Q., Cheng, B., et al. (2011). Genome-wide analysis of the auxin response factor (ARF) gene family in maize (*Zea mays*). *Plant Growth Regul.* 63, 225–234. doi: 10.1007/s10725-010-9519-0
- Luo, X.-C., Sun, M.-H., Xu, R. R., Shu, H.-R., Wang, J. W., and Zhang, S.-Z. (2014). Genomewide identification and expression analysis of the ARF gene family in apple. *J. Genet.* 93, 785–797. doi: 10.1007/s12041-014-0462-0
- Mockaitis, K., and Estelle, M. (2008). Auxin receptors and plant development: a new signaling paradigm. *Annu. Rev. Cell Dev. Biol.* 24, 55–80. doi: 10.1146/annurev.cellbio.23.090506.123214
- Mun, J.-H., Yu, H.-J., Shin, J. Y., Oh, M., Hwang, H.-J., and Chung, H. (2012). Auxin response factor gene family in Brassica rapa: genomic organization, divergence, expression, and evolution. *Mol. Genet. Genomics* 287, 765–784. doi: 10.1007/s00438-012-0718-4
- Okushima, Y., Overvoorde, P. J., Arima, K., Alonso, J. M., Chan, A., Chang, C., et al. (2005). Functional genomic analysis of the AUXIN RESPONSE FACTOR gene family members in *Arabidopsis thaliana*: unique and overlapping functions of ARF7 and ARF19. *Plant Cell* 17, 444–463. doi: 10.1105/tpc.104.028316
- Pekker, I., Alvarez, J. P., and Eshed, Y. (2005). Auxin response factors mediate *Arabidopsis* organ asymmetry via modulation of KANADI activity. *Plant Cell* 17, 2899–2910. doi: 10.1105/tpc.105.034876
- Piya, S., Shrestha, S. K., Binder, B., Stewart, C. N. Jr., and Hewezi, T. (2014). Protein-protein interaction and gene co-expression maps of ARFs and Aux/IAAs in *Arabidopsis*. *Front. Plant Sci.* 5:744. doi: 10.3389/fpls.2014.00744
- Rademacher, E. H., Lokerse, A. S., Schlereth, A., Llavata-Peris, C. I., Bayer, M., Kientz, M., et al. (2012). Different auxin response machineries control distinct cell fates in the early plant embryo. *Dev. Cell* 22, 211–222. doi: 10.1016/j.devcel.2011.10.026

- Rademacher, E. H., Möller, B., Lokerse, A. S., Llavata-Peris, C. I., van den Berg, W., and Weijers, D. (2011). A cellular expression map of the *Arabidopsis* AUXIN RESPONSE FACTOR gene family. *Plant J.* 68, 597–606. doi: 10.1111/j.1365-313X.2011.04710.x
- Rhoades, M. W., Reinhart, B. J., Lim, L. P., Burge, C. B., Bartel, B., and Bartel, D. P. (2002). Prediction of plant microRNA targets. *Cell* 110, 513–520. doi: 10.1016/S0092-8674(02)00863-2
- Rosado, A., Li, R., Van de Ven, W., Hsu, E., and Raikhel, N. V. (2012). *Arabidopsis* ribosomal proteins control developmental programs through translational regulation of auxin response factors. *Proc. Natl. Acad. Sci. U.S.A.* 109, 19537–19544. doi: 10.1073/pnas.1214774109
- Sagar, M., Chervin, C., Mila, I., Hao, Y., Roustan, J.-P., Benichou, M., et al. (2013). *SIARF4*, an auxin response factor involved in the control of sugar metabolism during tomato fruit development. *Plant Physiol.* 161, 1362–1374. doi: 10.1104/pp.113.213843
- Salehin, M., Bagchi, R., and Estelle, M. (2015). SCFTIR1/AFB-based auxin perception: mechanism and role in plant growth and development. *Plant Cell* 27, 9–19. doi: 10.1105/tpc.114.133744
- Sessions, A., Nemhauser, J. L., McColl, A., Roe, J. L., Feldmann, K. A., and Zambryski, P. C. (1997). *ETTIN* patterns the *Arabidopsis* floral meristem and reproductive organs. *Development* 124, 4481–4491.
- Shen, C., Yue, R., Sun, T., Zhang, L., Xu, L., Tie, S., et al. (2015a). Genome-wide identification and expression analysis of auxin response factor gene family in *Medicago truncatula*. *Front. Plant Sci.* 6:73. doi: 10.3389/fpls.2015.00073
- Shen, C., Yue, R., Sun, T., Zhang, L., Yang, Y., and Wang, H. (2015b). *OsARF16*, a transcription factor regulating auxin redistribution, is required for iron deficiency response in rice (*Oryza sativa* L.). *Plant Sci.* 231, 148–158. doi: 10.1016/j.plantsci.2014.12.003
- Shin, R., Burch, A. Y., Huppert, K. A., Tiwari, S. B., Murphy, A. S., Guilfoyle, T. J., et al. (2007). The *Arabidopsis* transcription factor MYB77 modulates auxin signal transduction. *Plant Cell* 19, 2440–2453. doi: 10.1105/tpc.107.050963
- Su, Y. H., Liu, Y. B., Bai, B., and Zhang, X. S. (2014). Establishment of embryonic shoot–root axis is involved in auxin and cytokinin response during *Arabidopsis* somatic embryogenesis. *Front. Plant Sci.* 5:792. doi: 10.3389/fpls.2014.00792
- Sun, R., Wang, K., Guo, T., Jones, D. C., Cobb, J., Zhang, B., et al. (2015). Genome-wide identification of auxin response factor (*ARF*) genes and its tissue-specific prominent expression in *Gossypium raimondii*. *Funct. Integr. Genomics* 15, 481–493. doi: 10.1007/s10142-015-0437-0
- Szemenyei, H., Hannon, M., and Long, J. A. (2008). TOPLESS mediates auxin-dependent transcriptional repression during *Arabidopsis* embryogenesis. *Science* 319, 1384–1386. doi: 10.1126/science.1151461
- Tiwari, S. B., Hagen, G., and Guilfoyle, T. (2003). The roles of auxin response factor domains in auxin-responsive transcription. *Plant Cell* 15, 533–543. doi: 10.1105/tpc.008417
- Ulmasov, T., Hagen, G., and Guilfoyle, T. J. (1997). ARF1, a transcription factor that binds to auxin response elements. *Science* 276, 1865–1868. doi: 10.1126/science.276.5320.1865
- Ulmasov, T., Hagen, G., and Guilfoyle, T. J. (1999). Dimerization and DNA binding of auxin response factors. *Plant J.* 19, 309–319. doi: 10.1046/j.1365-313X.1999.00538.x
- Van Ha, C., Le, D. T., Nishiyama, R., Watanabe, Y., Sulieman, S., Tran, U. T., et al. (2013). The auxin response factor transcription factor family in soybean: genome-wide identification and expression analyses during development and water stress. *DNA Res.* 20, 511–524. doi: 10.1093/dnares/dst027
- Varaud, E., Brioudes, F., Szécsi, J., Leroux, J., Brown, S., Perrot-Rechenmann, C., et al. (2011). AUXIN RESPONSE FACTOR8 regulates *Arabidopsis* petal growth by interacting with the bHLH transcription factor BIGPETALp. *Plant Cell* 23, 973–983. doi: 10.1105/tpc.110.081653
- Vert, G., Walcher, C. L., Chory, J., and Nemhauser, J. L. (2008). Integration of auxin and brassinosteroid pathways by Auxin Response Factor 2. *Proc. Natl. Acad. Sci. U.S.A.* 105, 9829–9834. doi: 10.1073/pnas.0803996105
- Wan, S., Li, W., Zhu, Y., Liu, Z., Huang, W., and Zhan, J. (2014). Genome-wide identification, characterization and expression analysis of the auxin response factor gene family in *Vitis vinifera*. *Plant Cell Rep.* 33, 1365–1375. doi: 10.1007/s00299-014-1622-7
- Wang, D., Pei, K., Fu, Y., Sun, Z., Li, S., Liu, H., et al. (2007). Genome-wide analysis of the auxin response factors (*ARF*) gene family in rice (*Oryza sativa*). *Gene* 394, 13–24. doi: 10.1016/j.gene.2007.01.006
- Wang, J.-W., Wang, L.-J., Mao, Y.-B., Cai, W.-J., Xue, H.-W., and Chen, X.-Y. (2005). Control of root cap formation by microRNA-targeted auxin response factors in *Arabidopsis*. *Plant Cell* 17, 2204–2216. doi: 10.1105/tpc.105.033076
- Wang, R., and Estelle, M. (2014). Diversity and specificity: auxin perception and signaling through the TIR1/AFB pathway. *Curr. Opin. Plant Biol.* 21, 51–58. doi: 10.1016/j.pbi.2014.06.006
- Wang, S., Zhang, S., Sun, C., Xu, Y., Chen, Y., Yu, C., et al. (2014). Auxin response factor (*OsARF12*), a novel regulator for phosphate homeostasis in rice (*Oryza sativa*). *New Phytol.* 201, 91–103. doi: 10.1111/nph.12499
- Wang, Y., Li, K., Chen, L., Zou, Y., Liu, H., Tian, Y., et al. (2015). microRNA167-directed regulation of the auxin response factors, *GmARF8a* and *GmARF8b*, is required for soybean (*Glycine max* L.) nodulation and lateral root development. *Plant Physiol.* 168, 984–999. doi: 10.1104/pp.15.00265
- Williams, L., Carles, C. C., Osmont, K. S., and Fletcher, J. C. (2005). A database analysis method identifies an endogenous trans-acting short-interfering RNA that targets the *Arabidopsis* *ARF2*, *ARF3*, and *ARF4* genes. *Proc. Natl. Acad. Sci. U.S.A.* 102, 9703–9708. doi: 10.1073/pnas.0504029102
- Wilmoth, J. C., Wang, S., Tiwari, S. B., Joshi, A. D., Hagen, G., Guilfoyle, T. J., et al. (2005). *NPH4/ARF7* and *ARF19* promote leaf expansion and auxin-induced lateral root formation. *Plant J.* 43, 118–130. doi: 10.1111/j.1365-313X.2005.02432.x
- Wu, J., Wang, F., Cheng, L., Kong, F., Peng, Z., Liu, S., et al. (2011). Identification, isolation and expression analysis of auxin response factor (*ARF*) genes in *Solanum lycopersicum*. *Plant Cell Rep.* 30, 2059–2073. doi: 10.1007/s00299-011-1113-z
- Yu, H., Soler, M., Mila, I., San Clemente, H., Savelli, B., Dunand, C., et al. (2014). Genome-wide characterization and expression profiling of the AUXIN RESPONSE FACTOR (*ARF*) gene family in *Eucalyptus grandis*. *PLoS ONE* 9:e108906. doi: 10.1371/journal.pone.0108906
- Zhang, S., Wang, S., Xu, Y., Yu, C., Shen, C., Qian, Q., et al. (2015a). The auxin response factor, *OsARF19*, controls rice leaf angles through positively regulating *OsGH3-5* and *OsBRI1*. *Plant Cell Environ.* 38, 638–654. doi: 10.1111/pce.12397
- Zhang, X., Yan, F., Tang, Y., Yuan, Y., Deng, W., and Li, Z. (2015b). Auxin response gene *SIARF3* plays multiple roles in tomato development and is involved in the formation of epidermal cells and trichomes. *Plant Cell Physiol.* 56, 2110–2124. doi: 10.1093/pcp/pcv136
- Zouine, M., Fu, Y., Chateigner-Boutin, A.-L., Mila, I., Frasse, P., Wang, H., et al. (2014). Characterization of the tomato *ARF* gene family uncovers a multi-levels post-transcriptional regulation including alternative splicing. *PLoS ONE* 9:e84203. doi: 10.1371/journal.pone.0084203

**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2016 Li, Xie, Hu and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.