Plant Knowledge Journal
ISSN: 2200-5390
EISSN: 2200-5404
2(2): 69-75 (2013)

Southern Cross Publishing Group
Australia

Regulation of core cell cycle genes by cis-regulatory elements in *Arabidopsis thaliana*

Ehsan Sadegh Nejad, Hossein Askari*, Sara Hamzelou, Morteza Gholami

Department of Biotechnology, Faculty of New Technologies Engineering, Shahid Beheshti University, G. C., Tehran, Iran

***Corresponding author: askarihossein@yahoo.com**

Abstract

Core cell cycle genes regulate the dividing cell to progress through the different phases of the cell cycle in response to environmental cues. The identification of cis-regulatory elements involved in complicated gene networks of core cell cycle genes can help to clear gene expression variation during Arabidopsis cell division cycle. We have found cis-acting upstream regulatory elements of core cell cycle-encoding genes with using PLACE and plantCARE databases. These databases analyzed the promoter regions of seventy five of the core genes and determined ci-regulatory elements. The upstream sequences of core cell cycle genes contain different regulatory groups such as light responsive element (LRE or L), stress responsive element (SRE or S), hormone-responsive element (HRE or H), elicitor specific responsive element (ESRE or E), expression regulation responsive element (ERRE or R), binding site specific responsive element (BSSRE or B), and plant tissue responsive element (PTRE or TS) which help in induction of gene expression during cell division and expansion. On the basis of analysis in the regulatory elements and experimental data, we confirm the functional responses of core cell cycle genes in plant *Arabidopsis thaliana*. We have also identified the presence of the most important elements under repetition frequency of them and genes number including cis-regulatory elements. The results indicated that correlation coefficient was the high (96%) in between these two parameters. The maximum upstream elements of core cell cycle genes are categorized in functional groups including light responsiveness (35.71%), abiotic stress (28.6), hormone (14.3%), and less than 0.01%of other groups. We concluded that the functional groups of cis-acting elements may collaborate with together and respond to environmental cues. The preparation of synthetic promoters using different motifs can develop manipulation of cell cycle with regulation of core genes expression through environmental signals.

Keywords: Cis-regulatory element; Core gene; Gene expression; Plant cell cycle; Transcriptional regulation.
Abbreviations: ABA- abscisic acid; APC- anaphase promoting complex; CDC- cell division cycle; CDK- cyclin-dependent kinase; CKS- cyclin kinase subunits; CYC- cyclin; DEL- DP-E2F-like; DP-dimerization partner; E2F- adenovirus E2 promoter-binding protein; G2/M- gap2/mitosis; G1/S-gap1/synthesis; JA-Jasmonic acid; KRP- kip-related proteins; MCM-minichromosome maintenance; MJ- methyl jasmonate; MSA- M-specific activators; ORC-origin recognition complex; ORF-open reading frame; Ub-ubiquitin.

Introduction

In spite of the importance of the migration and programmed cell death, cell division and expansion are fundamental biological processes which determine plant architecture and modulate growth rate in response to the environmental cues (Dupuy et al., 2010). On the other hand, developmental feature of plants is mainly established on the post-embryonic cell division (Combettes et al., 1999). Regulation of the Arabidopsis cell cycle critically intersects with the regulation of developmental programs (Wellmer and Riechmann, 2005) that necessarily manages the essential regulations through a complex gene network. The experimental results revealed that up to 1000 genes display cell cycle-regulated or –associated expression (Menges et al., 2002, 2003) and a wide range of cellular processes including hormone response, signal transduction, transcription control, and metabolic regulation have been marked to be cell cycle regulated processes in plants (White et al., 1999; Chen et al., 2002). Of the complex gene network,61 ones appear to formed the core cell-cycle genes where 23 genes were generally expressed in diving and young differentiating tissues, 34 genes mostly in both dividing and differentiated tissues, and 4 gene transcripts were primarily in differentiated tissues (Engler et al., 2009). In total, the core genes were classified in seven selected families of cell cycle regulators including cyclin-dependent kinases (CDKs), cyclins (CYC), CDK/cyclin interactors, dimerization partner (DP), adenovirus E2 promoter-binding protein (E2F), DP-E2F-like (DEL), and regulatory proteins (Vandepoele et al., 2002). In other classification, they were clustered at the seven family classes during cell cycle progression including CDKs, CYC, kip-related proteins (KRP), DNA synthesis, cell cycle regulators, cyclin kinase subunits (CKS) and proteasome (Engler et al., 2009). Cell cycle-regulated gene expression conducts key step in cell cycle control and consequently cell progression. Despite undeniable importance of post-transcriptional and post-translational regulation, the transcriptional regulation makes considerable controls on core cell cycle regulators (Menges et al., 2005). Cyclin-dependent kinases (CDKs) which govern the plant cell cycle show little dependence on transcriptional regulation (Inze´ and De Veylder, 2006), with the exception of the B-type CDK genes with an expression peak during G2 and M phases (Andersen et al., 2008), while

most cyclins exhibit striking oscillatory expression at the transcriptional level. The CYCA3 class is specifically expressed in the S phase, and other A-type and B-type cyclins largely showed common modulation in G2/M (Menges et al., 2005). Ito et al., (1998) and Tr´ehin et al., (1999) reported that the modulation of several M-phase-regulated genes was dependent on a conserved cis-acting element (MSA; M-specific activators) containing a central core pentamer with homology to Myb-binding sites that is responsible for the M-phase-specific regulation. In Arabidopsis, expression of S-phase-specific genes such as DNA polymerase α, origin recognition complex (ORC), minichromosome maintenance (MCM), and cell division cycle 6 (CDC6) was stimulated using combined overexpression of E2Fa/DPa transcription factors (De veylder et al., 2002). In contrast, a monomeric form of DEL proteins can repress the transcription of genes under E2F promoter control (Kosugi and Ohashi, 2002). The results suggest that there is the potential for transcriptional regulation of cell cycle related genes and with the basis, establishment of signaling networks responsible for molecular translation of environmental cues into the language of the genes makes a critical point in the cycle regulation. Reports demonstrated that intrinsic and extrinsic signals such as cytokinines (Zhang et al., 2005; Beeckman et al., 2001), auxin (John et al., 1993; Gray et al., 2001), gibberlines (Sauter et al.,1995), brassinostroids (Hu et al., 2000), abscisic acid (Wang et al., 1998), jasmonic acid (Swiatek et al., 2002; Oakenfull et al., 2002), sucrose (Van't Hof, 1966; Riou-Khamlichi et al., 2000; Oakenfullet al., 2002), light (del Pozo et al., 2002; Inze´, 2005), reactive oxygen species and redox (Reichheld et al., 1999)control cell cycle progression in the variety of situations. Here, we report our efforts to find candidate cis-regulatory elements present up to 1000bp upstream of 75 core cell cycle genes of *Arabidopsis thaliana* to further understand the regulation of core genes in plants in response to external and internal cues.

Result

Functional groups of cis-regulatory elements in core cell cycle genes

Our data has suggested a model of cis-regulatory elements frequency and their function in core cell cycle genes. We divided the total cis-acting elements of core cell cycle genes into two major groups including; cis elements responsible for internal and external cues (Supplementary Table 1). The cis-regulatory elements of each group are categorized to several sections according to their function. The cis elements responsible for internal cues are categorized into elements of hormonal responsiveness (HRE or H), expression regulation responsive element (ERRE or R), binding site specific responsive element (BSSRE or B) and plant tissue responsive element (PTRE or T), while the cis-regulatory elements involved in response to external conditions are embraced to elements of light responsive element (LRE or L), stress responsive element (SRE or S) and elicitor specific responsive element(ESRE or E) and circadian regulation. Light responsive elements were found at high frequency (62%) than other cis elements responsible for external cues. In addition, stress, elicitor, and circadian responsive elements presented at a frequency up to 30, 6, and 2 percent in promoter region of core cell cycle genes, respectively. While functional groups of responsive elements related to internal cues included HRE (37%), PTRE (31%), BSSRE (20%), and ERRE with frequency of 12 percent. This indicates that hormonal stimulators can be most important internal factors involved in regulation of core genes through regulatory region.

Occurrence rate of cis elements in promoter regions of core genes

We also selected fourteen elements as more abundant cis-regulatory elements in promoter regions of core cell cycle genes without mention of common cis-acting elements such as CAAT-box and TATA-box. The both of them have fundamental role in initiation of transcription process and are found in all the promoter regions of genes. The most important indexes for introduction of these elements were (1) the sum of each cis-regulatory element in promoter regions of 75 core cell cycle genes and (2) the number of genes including each element, that correlation coefficient was the high (96%) in between these two parameters. The occurrence of cis elements in all the seventy five core cell cycle genes is shown in Fig 1. The highest frequency of cis elements is related to ARE cis motifs (110 times) which were discovered in most of core genes involved in cell cycle regulation. After that 5UTR Py-rich stretch cis elements (99), G-Box(89), GT1-motif (87), Skn-1_motif (73), HSE (70), Box 4 (69), TCA-element (66) GARE-motif and Box I (59), Circadian (58), TC-rich repeats and MBS (56), GAG-motif cis elements (55)with high frequency and other cis elements were found less than 45 times in 75 gene promoter regions. The maximum upstream elements of core cell cycle genes are classified almost in all groups of our classification including light responsive element, circadian, stress, hormone, specific process and expression regulation. Among cis acting elements of different groups, GAG-motif, GT1-motif, G-Box, Box I and Box 4 involved in different wavelengths of light responsiveness. The circadian element (CIRC) and Skn-1_motif which are essential for the control circadian rhythm and endosperm expression, respectively, were seen in the most of core cell cycle genes. The upstream sequences of these genes also have cis-regulatory elements that they respond to abiotic stress such as drought inducibility (MBS), defence and stress responsiveness (TC-rich- repeats), heat stress responsive element (HSE) and anaerobic induction (ARE). Data obtained from promoter regions for all core genes of cell cycle introduced two hormones responsive elements as the maximum elements in between hormones responsive elements including, TCA-element involved in salicylic acid responsiveness and GARE involved in gibberellin-responsiveness. The 5-UTR Py-rich stretch-element was shown as special cis element which has fundamental role in high transcription levels of cell cycle genes. This data indicated that gene expression control in different checkpoints of cell cycle may be dependent to both

Table 1. Clustering result using k-means. We mentioned each cis-regulatory element based on its functional inside each group (mentioned in Supplementary Table 1). For example, L_1 is as a light responsive element that we used L as an abbreviation of light and numbered all cis-regulatory elements with same function.

	Samples in each cluster
Cluster(1)	S_13 S_15 C_1 C_2 C_3 T_11 H_4 H_6 H_13
Cluster(2)	L_1 L_2 L_3 L_4 L_5 L_6 L_7 L_8 L_9 L_10 L_11 L_12 L_13 L_14 L_15 L_16 L_17 L_18 L_19 L_21 L_22 L_23 L_24 L_25 L_26 L_27 L_28 L_29 L_30 L_31 S_3 S_4 S_5 S_6 S_8 S_9 S_10 S_14 E_1 E_2 E_3 T_1 T_2 T_3 T_4 T_5 T_6 T_7 T_8 T_9 T_10 R_3 R_4 H_1 H_3 H_5 H_7 H_8 H_9 H_11 H_12 B_1 B_2 B_3 B_4 B_5 B_6 B_7
Cluster(3)	L_20 S_1 H_2
Cluster(4)	S_2 S_7 S_11 S_12 R_1 R_2 H_10

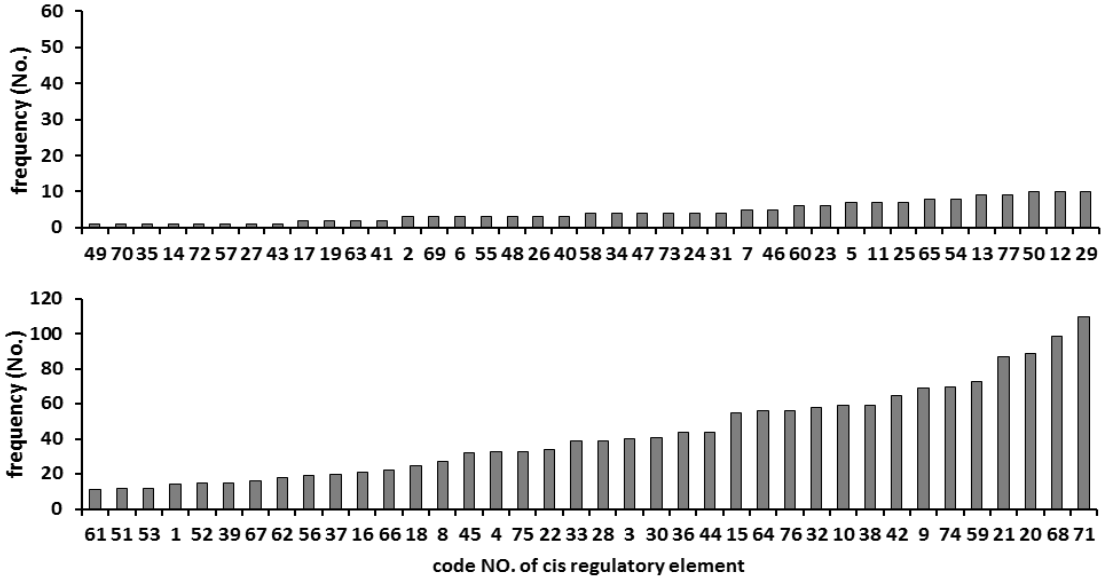

Fig 1. Frequency of cis-regulatory elements occurrence in seventy five core cell cycle genes upstream sequences of *Arabidopsis thaliana*. The horizontal axis indicates the number of cis-identifier related each cis-regulatory element (mentioned in Supplementary Table 1) and vertical axis shows frequency of each cis-regulatory element in promoter regions of core cell cycle genes in *Arabidopsis thaliana*.

the frequency of enhancers and stress responsive cis-regulatory elements under abnormal conditions.

Cluster analysis of cis-regulatory elements

The main objective in cluster analysis is the classification of objects according to similarity. Similar objects are in one cluster and dissimilar objects separate by assigning them to different clusters. One of the most popular clustering methods is K-Means clustering algorithm that we run the algorithm repeatedly with different values of k and compare the clustering results. In the end, we chose four clusters (k=4) in our dataset as the optimal number of clusters (Fig 2). Results from Table 1 demonstrate that cluster 1 has the highest number of cis-regulatory elements. It almost includes all functional groups of cis-regulatory elements. In addition, other clusters have different cis elements that they also response to external and internal cues.

What makes one cis-regulatory element dominant? The number or variety

Principal component analysis (PCA) has proposed to analyze data set of cis-regulatory elements involved in core cell cycle genes. PCA (Jolliffe, 1986) is a classical technique to find a small number of new variables by reducing the dimensionality of the data set that PCA will do it by summarizing the features of the data. The variety and distributions of cis-regulatory elements of core cell cycle genes in response to internal and external cues are shown in Fig 3. As a result, the cis-regulatory element variety and frequency can be critically important in attraction of transcription factors and they will cause the more transcripts of core genes in response to internal and external cues. This data set showed the relative extents of distribution of 77 cis-regulatory elements in promoter regions of 75 core genes in Arabidopsis cell cycle. With PCA, we could create a subset of the elements data (77 cis-regulatory elements) that were categorized into 8 temporal patterns according to their functional groups. Figure 4 is a visualization of this data in the space of the 2 Principal components (PC's), which contains 97.7% of the variation in the data. Each of the eight patterns is shown by a different color of shape. The eight patterns overlap with together in Fig4. In our studies, the cis elements responsible for especial functions such as stress, hormone, and circadian have the low variety, but their frequency and number of repetitions are the high. Of course, the high number of occurrences of cis-regulatory elements can compensate the low rate of cis elements variety in promoters and be effective in gene expression. Many cis

elements in promoter of core cell cycle genes belonged to light, although the light effects are classified to three branches including qualification, quantification, and wavelength rate. In total, multiplicity and variety of this short sequence in promoter of core genes lead to gene response according to the signaling intensity.

Discussion

Cell division is a constitutive process in meristem points of plant (Engler et al., 2009) and the amount of plant cell cycle gene transcripts varies at different stages of cell cycle (Menges et al., 2005). Cell cycle genes are widely studied and several core genes are well documented for regulation of plant cell cycle (Vandepoele et al., 2002). Plant cell division has been shown to control cell cycle in plants through two major different checkpoints including Gap1/Synthesis and Gap2/Mitosis (De Veylder et al., 2003). Arabidopsis plant over expresses 75 core genes (Engler et al., 2009;Vandepoele et al., 2002) that they are co-expressed in response to abiotic and biotic stimuli during different phases of cell cycle. It suggests that core genes play a role in the regulation of cell cycle and contribute to its basal management against environmental cues. Expression of core genes are induced by transcription factors through cis-regulatory elements (Menges et al., 2005) that each cis-regulatory element has a functional response. For example, E2Fa and E2Fb function as transcriptional activators and positive regulators of the cell cycle (De Veylder et al., 2002) and E2Fc acts as a transcriptional repressor and suppressor of cell division(del Pozo et al., 2002) that E2F target genes have an E2F cis-acting element in their promoter (E2F box). In addition, MSA-like sequences in B-type cyclin promoters from tobacco, soybean, and Arabidopsis may be a common cis-acting promoter element that controls M phase–specific expression of cell cycle–related genes in plants (Ito et al., 1998). Kip-Related Protein 1 (Arath; KRP1) expression as switching the cell cycle is activated by the phytohormone abscisic acid (Wang et al., 1998), suggesting that this particular KRP possess ABRE element and it is responsible for the cessation of cell cycle triggered with abscisic acid treatment. Recently, Nejad et al., (2012) demonstrated the presence of TGACG-motif element involved in the MeJA-responsiveness, located in KRPs gene promoter that might be responsible cessation of cell cycle in G1/S checkpoint. Light is a predominant factor in the control of many important biological processes during plant development and environmental responses such as growth, development, and stress responses in plants (Inze´, 2005).The highest frequency of light responsive elements can confirm that many environmental signals in plants are specifically adjusted by light conditions. In this study we found that all the upstream sequences of core cell cycle genes have light responsive cis elements which could have some roles in gene expression mechanism and control over expression of core genes during different phases of cell cycle. Plant hormones regulate the transcriptional expression of several cell cycle genes in complex regulatory network (del Pozo et al., 2005). Auxins and cytokinins are those best documented to be effective directly on cell cycle control. Auxin signal is caused the specific degradation of proteins through the ubiquitin (Ub) pathway (Dharmasiri and Estelle, 2002), which ultimately results in progression through the cell cycle. Anaphase promoting complex (APC) in plants affect cell division as a complex involved in degradation of proteins (Capron et al., 2003). The presence of auxin responsive element (TGA-

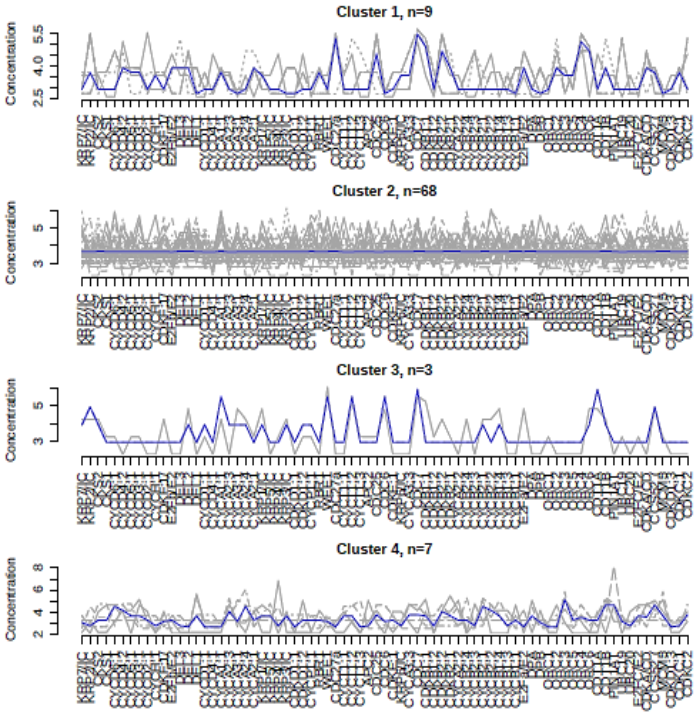

Fig 2. K-means cluster analysis. The x-axes are variable indices (core cell cycle genes) and y-axes are relative intensities (number of cis-acting elements). The blue lines represent median intensities of corresponding clusters.

element) in promoter region of APC can be a major cause in expression of this gene. The importance of Cytokinin as regulatory hormone in the promotion of cell division is not undeniable (Wang et al., 1981; Bayliss, 1985). In Arabidopsis, plant D cyclins especially CYCD3 are the key regulators of the G1/S transition of the cell cycle that exogenous cytokinins and sucrose stimulate expression of D-type cyclins (Riou-Khamlichi et al., 1999; Soni et al., 1995). Gibberelic acid, in addition, seems to stimulate cell division (Asahina et al., 2002). The variety of cis-regulatory elements involved in gibberellin-responsiveness such as TATC-box, P-box, and GARE-motif can confirm expression of core genes in cell cycle progression. Our finding from promoter regions for all core genes of cell cycle introduced GARE-motif as the maximum elements in between gibberellin responsive elements and other hormone responsive elements. On the other hand, Jasmonic acid (JA) and Absiscisc acid (ABA) have negative regulatory role in cell cycle progression on G1/S and G2/M transitions (Swiatek et al., 2002), but the molecular mechanism are not yet known. The core promoter regions of genes revealed the occurrence of SARE and TCA-involved in salicylic acid responsiveness, TGACG- & CGTCA involved in the MeJA-responsiveness, and ABRE involved in the abscisic acid responsiveness. Shinozaki et al., (2003) demonstrated that ABRE has important role in adapting vegetative tissues to abiotic stresses such as drought and high salinity. In addition, Ethylene as endogenous and stress hormone acts during adverse biotic and abiotic conditions (Bleecker and Kende, 2000). An 8-nucleotide ERE (ATTTCAAA) was seen in the promoters of various genes especially DEL1 and DEL3 that are ethylene-inducible contain EREs and inhibit plant cell cycle on G1/S transition.

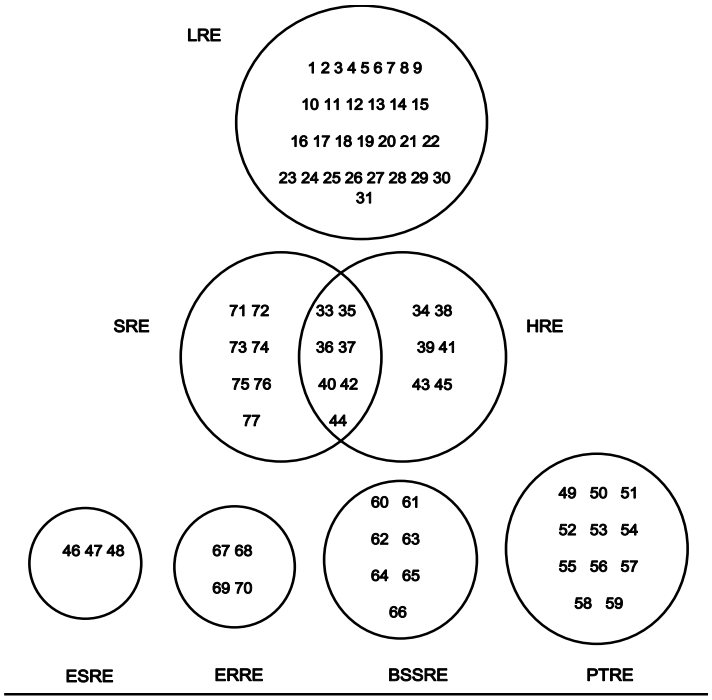

Fig 3. Classification of cis-regulatory elements according to variety and distributions of them in promoter regions of core cell cycle genes of *Arabidopsis thaliana*. This figure was designed according to Supplementary Table 1. Each cis-regulatory element receives a code number and it is utilized in each circle of our classification. The size of circle indicates the frequency rate of distribution of cis-regulatory elements in promoter regions of core genes. For example, light responsive elements (LRE or L) (large circle) present at high frequency than other cis elements and elicitor specific responsive elements (ESRE or E) (small circle) have low variety in the analyzed 75 sequences.

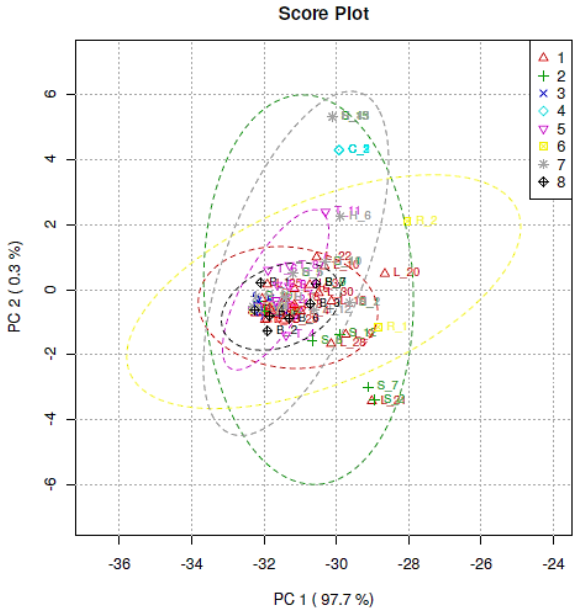

Fig 4. Score plot showed the visualization of a subset of the cis-regulatory elements data involved in Arabidopsis core cell cycle genes. With PCA, functional groups of cis-regulatory elements were categorized into 8 temporal patterns that each of the eight patterns was shown by a different color of shape including; 1:light (red), 2: stress (green), 3:elicitor (blue), 4:circadian (light blue), 5:tissue (purple), 6:regulation (yellow), 7:hormone (gray), 8:binding site (black).

The important biological processes when exposed to biotic stress, will activate the transduction pathway which is usually carried out by signaling molecules such as SA, JA, Ethylene, and ABA (Durrant and Dong, 2004; Lorenzo and Solano, 2005; van Loon et al., 2006), although core cell cycle genes possess three elicitor-responsive elements including AT-rich sequence, EIRE, and ELI-box3 that they can control cell division in response to biotic stress. The cis elements presented in Supplementary Table 1 are known to perform different functions in plant cell division and expansion through regulation of gene expression in response to internal and external cues. However, molecular details of how these motifs interact to bring out combinatorial regulation are largely not clear. Hopefully, preparation of synthetic promoters using different motifs individually or in combinations for regulating the expression of core cell cycle genes can develop manipulation of cell cycle during different phases through outs cues.

Materials and methods

Selection of core cell cycle genes

Studies of Engler et al., (2009) detected the core cell cycle genes of *Arabidopsis thaliana* that we used them as a set of genes to find the cis-regulatory elements.

Promoter finding

The core cell-cycle genes of *Arabidopsis thaliana* were submitted to NCBI (http://www.ncbi.nlm. nih.gov/) (Wheeler et al., 2005) and their mRNA sequences acquired. Translation start site for each open reading frame (ORF) was determined. Each ORF was blasted against Arabidopsis genome and 1000 bp upstream of that, assumed as promoter region.

Identification of regulatory motif

We used plantCARE (http://bioinformatics.psb.ugent.be/ webtools/plantcare/html) (Lescot et al., 2002) and PLACE (http://www.dna.affrc.go.jp/PLACE) (Higo et al., 1999) to achieve cis-regulatory elements which occur in the promoter region and regulate the cell division process in different phases.

Cluster analysis of cis-regulatory elements

Classification analysis was done on cis-regulatory elements of Arabidopsis core cell cycle genes. K-means clustering were performed using Cluster software version 2.11 (http://rana.lbl.gov/EisenSoftware.htm) (Eisen et al., 1998).

Statistical analysis

We created a data matrix that rows represented cis-regulatory elements and column represents core cell cycle genes. We used the Principal components analysis (PCA) for performing the analysis on the data set (Clark and Ma'ayan 2011). This analysis was done using web based MetaboAnalyst (http://www. metaboanalyst.ca) and produced a detailed analysis report.

Conclusion

The most important functional groups of cis-acting elements were introduced that they can regulate cell cycle progression through regulatory factors such as transcription factors. In addition, the low number of cis-regulatory elements with determined function in promoter sequences may cause the low affinity the assembly of transcription factors that play the important role in the gene expression. Instead, the increased frequencies of cis-regulatory elements may follow the sensitive behavior of promoter in response to environmental signals. This information helps us to manipulate the cell cycle through preparation of synthetic promoters using different motifs for regulating the expression of core cell cycle genes in response to environmental cues.

Acknowledgements

We sincerely thank all past and current members of the plant biotechnology group of the Department of Agricultural Biotechnology for their continuous efforts to unravel the new light of biology science.

Supplementary data available online

References

Andersen SU, Buechel S, Zhao Z, Ljung K, Nova´ k O, Busch W, Schuster C, Lohmann JU (2008) Requirement of B2-type cyclin dependent kinases for meristem integrity in *Arabidopsis thaliana*. Plant Cell. 20:88–100

Asahina M, Iwai H, Kikuchi A, Yamaguchi S, Kamiya Y, Kamada H, Satoh S (2002) Gibberellin produced in the cotyledon is required for cell division during tissue reunion in the cortex of cut cucumber and tomato hypocotyls. Plant Physiol. 129:201–210

Bayliss MW (1985) Regulation of the cell division cycle in plants. In: Bryant JA, Francis D (eds). The Cell Division Cycle in Plants. Cambridge University Press, Cambridge, pp 157–177

Beeckman T, Burssens S, Inze D (2001) The peri-cell-cycle in Arabidopsis. J Exp Bot. 52:403–411

Bleecker AB, Kende H (2000) Ethylene: a gaseous signal molecule in plants. Annu Rev Cell Dev Bi. 16:1–18

Capron A, Serralbo O, Fulop K, Frugier F, Parmentier Y, Dong A, Lecureuil A, Guerche P, Kondorosi E, Scheres B, Genschik P (2003) The Arabidopsis anaphase-promoting complex or cyclosome: molecular and genetic characterization of the APC2 subunit. Plant Cell. 15:2370–2382

Chen WQ, Provart NJ, Glazebrook J, Katagiri F, et al (2002) Expression profile matrix of Arabidopsis transcription factor genes suggests their putative functions in response to environmental stresses. Plant Cell. 14:559-574

Clark NR, Ma'ayan A (2011) Introduction to statistical methods to analyze large data sets: Principal components analysis. Sci Signal. 4(190), tr3. doi:10.1126/scisignal.2001967

Combettes B, Reichheld JP, Chaboute´ ME, Philips G, Shen WH, Chaubet-Gigot N (1999) Study of phase-specific gene expression in synchronized tobacco cells. Methods Cell Sci. 21:109–121

De Veylder L, Beeckman T, Beemster GT, de Almeida Engler J, Ormenese S, Maes S, Naudts M, Van Der Schueren E, Jacqmard A, Engler G, Inze D (2002) Control of proliferation, endoreduplication and differentiation by the Arabidopsis E2Fa-DPa transcription factor. EMBO J. 21:1360–1368

De Veylder L, Joube` s J, Inze´ D (2003) Plant cell cycle transitions. Curr Opin Plant Biol. 6:536–543

Del Pozo JC, Boniotti MB, Gutierrez C (2002) Arabidopsis E2Fc functions in cell division and is degraded by the ubiquitin-SCFAtSKP2 pathway in response to light. Plant Cell. 14:3057–3071

del Pozo JC, Lopes-Matas A, Ramirez-Parra E, Gutierrez C (2005) Hormonal control of the plant cell cycle. Physiol Planta. 123:173–183

Dharmasiri S, Estelle M (2002) The role of regulated protein degradation in auxin response. Plant Mol Biol. 49:401–409

Dupuy L, Mackenzie J, Haseloff J (2010) Coordination of plant cell division and expansion in a simple morphogenetic system. Proc Natl Acad Sci USA. 107(6):2711–2716

Durrant WE, Dong X (2004) Systemic acquired resistance. Annu Rev Phytopathol. 42:185–209

Eisen M B, Spellman PT, Brown PO, Botstein D (1998) Cluster analysis and display of genome-wide expression patterns. Proc Natl Acad Sci USA. 95:14863–14868

Engler Jde A, De Veylder L, De Groodt R, Rombauts S, Boudolf V, De Meyer B, Hemerly A, Ferreira P, Beeckman T, Karimi M, Hilson P, Inze´ D, Engler G (2009) Systematic analysis of cell-cycle gene expression during Arabidopsis development. Plant J. 59(4):645-660

Gray WM, Kepinski S, Rousse D, Leyser O, Estelle M (2001) Auxin regulates SCF (TIR1)-dependent degradation of AUX/IAA proteins. Nature. 414:271–276

Higo K, Ugawa Y, Iwamoto M, Korenaga T (1999) Plant cis-acting regulatory DNA elements (PLACE) database. Nucleic Acids Res. 27(1):297-300

Hu Y, Bao F, Li J (2000) Promotive effect of brassinosteroids on cell division involves a distinct CycD3-induction pathway in Arabidopsis. Plant J. 24:693–701

Inze´ D (2005) Green light for the cell cycle. EMBO J. 24:657–662

Inze´ D, De Veylder L (2006) Cell cycle regulation in plant development. Annu Rev Genet. 40:77–105

Ito M (1998) Cell cycle dependent gene expression. In: Francis D, Dudits D,Inze D (eds). Plant cell division. Colchester, UK: Portland Press, pp 187–206

John PCL, Zhang JK, Dong C, Diederich L, Wightman F (1993) p34cdc2 related proteins in control of cell cycle progression, the switch between division and differentiation in tissue development, and stimulation of division by auxin and cytokinin. Aust J Plant Physiol. 20:503–526

Jolliffe IT (1986) principle component analysis. Springer, New York

Kosugi S, Ohashi Y (2002) Interaction of the Arabidopsis E2F and DP proteins confers their concomitant nuclear translocation and transactivation. Plant Physiol. 128:833–843

Lescot M, Dehais P, Thijs G, Marchal K, Moreau Y, Van de Peer Y, Rouze P, Rombauts S (2002) Plant CARE, a database of plant cis-acting regulatory elements and a portal to tools for the in silico analysis of promoter sequences. Nucleic Acids Res. 30:325-327

Lorenzo O, Solano R (2005) Molecular players regulating the jasmonate signaling network. Curr Opin Plant Biol. 8:532–540

Menges M, de Jager SM, Gruissem W, Murray JA (2005) Global analysis of the core cell cycle regulators of Arabidopsis identifies novel genes, reveals multiple and highly specific profiles of expression and provides a coherent model for plant cell cycle control. Plant J. 41:546–566

Menges M, Hennig L, Gruissem W, Murray JA (2002) Cell cycle-regulated gene expression in Arabidopsis. J Biol Chem. 27741987–42002

Menges M, Hennig L, Gruissem W, Murray JA (2003) Genome-wide gene expression in an Arabidopsis cell suspension. Plant Mol Biol. 53:423–442

Nejad ES, Askari H, Soltani S (2012) Regulatory TGACG-motif may elicit the secondary metabolite production through inhibition of active Cyclin-dependent kinase/Cyclin complex. Plant Omics J. 5(6):553-558

Oakenfull EA, Riou-Khamlichi C, Murray JAH (2002) Plant D-type cyclins (CycDs) and the control of G1 progression. Philos T Roy Soc B. 357:749–60

Reichheld JP, Vernoux T, Lardon F, Van Montagu M, Inze D (199) Specific checkpoints regulate plant cell cycle progression in response to oxidative stress. Plant J. 17:647–56

Riou-Khamlichi C, Huntley R, Jacqmard A, Murray JA (1999) Cytokinin activation of Arabidopsis cell division through a D-type cyclin. Science. 283:1541–1544

Riou-Khamlichi C, Menges M, Healy JM, Murray JAH (2000) Sugar control of the plant cell cycle: differential regulation of Arabidopsis D-type cyclin gene expression. Mol Cell Biol. 20:4513–4521

Sauter M, Mekhedov SL, Kende H (1995) Gibberellin promotes histone H1 kinase activity and the expression of cdc2 and cyclin genes during the induction of rapid growth in deep water rice internodes. Plant J. 7:623–632

Shinozaki K, Shinozaki Y, Seki M (2003) Regulatory network of gene expression in the drought and cold stress reponses. Curr Opin Plant Biol. 6:410–417

Soni R, Carmichael JP, Shah ZH, Murray JA (1995) A family of cyclin D homologs from plants differentially controlled by growth regulators and containing the conserved retinoblastoma protein interaction motif. Plant Cell. 7:85–103

Swiatek A, Lenjou M, Van Bockstaele D, Inze D, Van Onckelen H (2002) Differential effect of jasmonic acid and abscisic acid on cell cycle progression in tobacco BY-2 cells. Plant Physiol.128:201–211

Tr´ehin C, Glab N, Perennes C, Planchais S, Bergounioux B (1999) M phase-specific activation of the *Nicotiana sylvestris* cyclin B1 promoter involves multiple regulatory elements. Plant J. 17:263–273

Vandepoele K, Raes J, De Veylder L, Rouze´ P, Rombauts S, Inze´ D (2002) Genome-wide analysis of core cell cycle genes in Arabidopsis. Plant Cell. 14:903–916

van Loon LC, Geraats BPJ, Linthorst HJM (2006) Ethylene as a modulator of disease resistance in plants. Trends Plant Sci. 11:184–191

Van't Hof J (1966) Experimental control of DNA synthesising and dividing cells in excised root tips of Pisumsativum. Am J Bot. 53:970–976

Wang H, Qi Q, Schorr P, Cutler AJ, Crosby WL, Fowke LC (1998) ICK1, a cyclin-dependent protein kinase inhibitor from *Arabidopsis thaliana* interacts with both Cdc2a and CycD3, and its expression is induced by abscisic acid. Plant J. 15(4):501-510

Wang TL, Everett NP, Gould AR, Street HP (1981) Studies on the control of the cell cycle in cultured plant cells. Protoplasma. 106(1-2):23–35

Wellmer F, Riechmann JL (2005) Gene network analysis in plant development by genomic technologies. Int J Dev Biol. 49(5-6):745-759

Wheeler DL, Church DM, Edgar R, Federhen S, Helmberg W, Madden TL, Pontius JU, Schuler GD, Schriml LM, Sequeira E, et al. (2005) Database resources of the National Center for Biotechnology Information: update. Nucleic Acids Res. 33(D39–D45). doi:10.1093/nar/gkl1031

White KP, Rifkin SA, Hurban P, Hogness DS (1999) Microarray analysis of Drosophila development during metamorphosis. Science. 286:2179–2184

Zhang K, Diederich L, John PC (2005) The cytokinin requirement for cell division in cultured *Nicotiana plumbaginifolia* cells can be satisfied by yeast Cdc25 protein tyrosine phosphatase: implications for mechanisms of cytokinin response and plant development. Plant Physiol. 137:308–316