Current Plant Biology 1 (2014) 55–59

Contents lists available at ScienceDirect

Current Plant Biology

journal homepage: www.elsevier.com/locate/cpb

Evolution of endogenous non-retroviral genes integrated into plant genomes

Hyosub Chu, Yeonhwa Jo, Won Kyong Cho*

Department of Agricultural Biotechnology, College of Agriculture and Life Sciences, Seoul National University, Seoul 151-921, Republic of Korea

ARTICLE INFO

Article history:
Received 9 May 2014
Received in revised form 29 July 2014
Accepted 29 July 2014

Keywords:
Evolution
Horizontal gene transfer
Integration
Non-retroviral
Plant
Virus

ABSTRACT

Numerous comparative genome analyses have revealed the wide extent of horizontal gene transfer (HGT) in living organisms, which contributes to their evolution and genetic diversity. Viruses play important roles in HGT. Endogenous viral elements (EVEs) are defined as viral DNA sequences present within the genomes of non-viral organisms. In eukaryotic cells, the majority of EVEs are derived from RNA viruses using reverse transcription. In contrast, endogenous non-retroviral elements (ENREs) are poorly studied. However, the increasing availability of genomic data and the rapid development of bioinformatics tools have enabled the identification of several ENREs in various eukaryotic organisms. To date, a small number of ENREs integrated into plant genomes have been identified. Of the known non-retroviruses, most identified ENREs are derived from double-strand (ds) RNA viruses, followed by single-strand (ss) DNA and ssRNA viruses. At least eight virus families have been identified. Of these, viruses in the family *Partitiviridae* are dominant, followed by viruses of the families *Chrysoviridae* and *Geminiviridae*. The identified ENREs have been primarily identified in eudicots, followed by monocots. In this review, we briefly discuss the current view on non-retroviral sequences integrated into plant genomes that are associated with plant-virus evolution and their possible roles in antiviral resistance.

Contents

1. Introduction

Viruses are infectious agents with small genome sizes that can only complete their life cycles within the living host cells of organisms of the three domains of eukaryotes, archaea, and bacteria [1]. With recent, rapid advances in the genomic analysis of viruses and hosts, it is now possible to trace the origins and evolution of viruses along with those of their hosts [1]. Horizontal gene transfer (HGT), or lateral gene transfer, is defined as the flow of genes between different species [2]. Numerous comparative genome analysis studies have revealed the wide extent of HGT in living organisms [3,4]. In particular, viruses play important roles in HGT, which contributes to the evolution and genetic diversity of living organisms.

Endogenous viral elements (EVEs) are defined as viral DNA sequences present within the genomes of non-viral organisms [5,6]. EVEs can consist of an entire viral genome or only a partial fragment.

* Corresponding author. Tel.: +82 2 880 4687; fax: +82 2 873 2317.
E-mail address: wonkyong@gmail.com (W.K. Cho).

http://dx.doi.org/10.1016/j.cpb.2014.07.002

In eukaryotic cells, the majority of EVEs are derived from RNA viruses that use reverse transcription (RT), such as retroviruses [7,8]. In particular, plant genomes harbor a large number of endogenous plant endogenous pararetroviruses (EPRVs), as demonstrated in several recent studies [8]. EPRVs are double-stranded (ds) DNA viruses belonging to the family *Caulimoviridae* [8]. They are widely distributed in the genomes of plants, including banana, petunia, potato, rice, and tobacco [8]. A recent study revealed the genome-wide integration of endogenous banana streak virus (BSA) with 24 loci spanning 10 chromosomes; however, endogenous BSA does not appear able to form free infectious viral particles [9].

In contrast to EVEs, endogenous non-retroviral elements (ENREs) have not been well studied. However, the increasing availability of genomic data as well as the rapid development of several bioinformatics tools have enabled the identification of several ENREs in various eukaryotic organisms, including animals, insects, plants, and fungi [6,10–14]. Here, we briefly review the current view of non-retroviral sequences integrated into plant genomes associated with plant-virus evolution.

2. Approaches for identifying ENREs integrated into plant genomes

Initial efforts to identify ENREs were very difficult without any information on host genomes. The general approaches for identifying ENREs are depicted in Fig. 1. Using viral sequences as probes, cross-hybridization based approaches have been predominantly used, such as Southern blot and Western blot analyses [15,16]. For example, Southern blot analysis has been useful for estimating the copy number of a geminivirus-related DNA (GRD) in the tobacco genome [15]. With the increasing availability of genomic data for viruses and hosts, it is now possible to screen ENREs within entire genomes using BLAST tools against databases, such as the nucleotide collection (NT), genome (chromosome), reference genomic sequence (refseq_genomic), genomic survey sequence (GSS), high-throughput genomic sequence (HTGS), and whole genome shotgun (WGS) databases of the National Center for Biotechnology Information (NCBI). Indeed, most recent studies have performed intensive BLAST searches using sequences of single strand (ss) DNA and dsRNA viruses as queries [10,17–19]. It is important to generate appropriate algorithms for BLAST searches and *E*-values for thresholds. Generally, virus-like sequences have been identified at the protein level, suggesting that commonly used *E*-values for blastp, blastx, tblastn, and tblastx matches were less than 1E−5 or 1E−6. The expression of identified sequences could be verified by polymerase chain reaction (PCR) or reverse transcription (RT)-PCR followed by cloning and sequencing based on available sequences for the virus and the host. In addition, phylogenetic analysis using identified protein sequences can reveal the phylogenetic relationships of ENREs and host proteins and can provide clues regarding the evolution of ENREs along with host genes. Furthermore, the ratio of nonsynonymous (K_a) to synonymous (K_s) nucleotide substitution rates has been widely used as a measure of selective pressure on protein sequences [17]. Calculation of the K_a/K_s ratio for ENREs has provided information on their expression but also suggests that the ENREs of interest were under purifying selection. The last step in identifying ENREs might be the characterization of the functional roles of ENREs in plant genomes, which could require considerable effort and time.

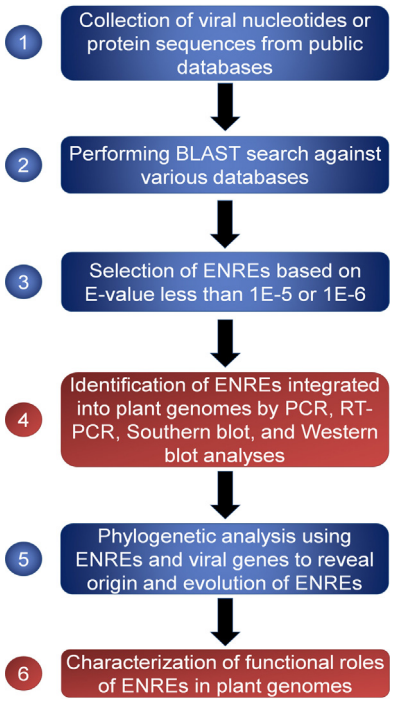

Fig. 1. Experimental approaches for identifying ENREs integrated into plant genomes. Studies identifying ENREs can be divided into two types: dry (blue box), which use various bioinformatics tools, and wet, which use laboratory experiments (red box).

3. Integration of ENREs into plant genomes

3.1. Overview of identified ENREs

To date, a small number of ENREs integrated into plant genomes have been identified. Here, we summarize these previous results (Fig. 2 and Supplementary Table 1) before describing them in detail. Of the known non-retroviruses, most identified ENREs are derived from dsRNA viruses, followed by ssDNA and ssRNA viruses (Fig. 2A). At least eight virus families have been identified. Of these, viruses in the family *Partitiviridae* are dominant, followed by those of the families *Chrysoviridae* and *Geminiviridae* (Fig. 2B). Viruses of at least 11 genera were identified that are integrated into plant genomes. Of these, unclassified viruses and partitiviruses are dominant (Fig. 2C). Identified ENREs have primarily been found in eudicots, followed by monocots. Even plants belonging to the classes Pinopsida and Prasinophyceae harbor ENREs (Fig. 2D). ENREs have been frequently identified in plants belonging to the orders Poales, Brassicales and Fabales (Fig. 2E). Some ENREs have been found to display high similarity with viral sequences. For example, 10 ENREs have been identified with an *E*-value of 0 (Fig. 2F).

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.cpb.2014.07.002.

3.2. Integration of sequences derived from dsRNA viruses in plant genomes

Among the various types of viruses, double-stranded (ds) RNA viruses have been frequently reported as giving rise to ENREs [10,17]. Interestingly, most dsRNA viruses homologous to plant genes are mycoviruses, which infect various fungi. For instance, the capsid protein (CP) of *Sclerotinia sclerotiorum* partitivirus S (SsPV-S) is homologous to the *Arabidopsis* protein IAA-leucine-resistant protein 2 (ILR2) [17]. Additionally, both the CPs of SsPV-S and ILR2 show high levels of similarity with a GEM protein of the meadow fescue (*Festuca pratensis*).

Using the protein sequences of available partitiviruses and totiviruses, a total of 22 partitivirus-like and 34 totivirus-like sequences have been found in various eukaryotic organisms, including plants [17]. Partitivirus-related ENREs have been found

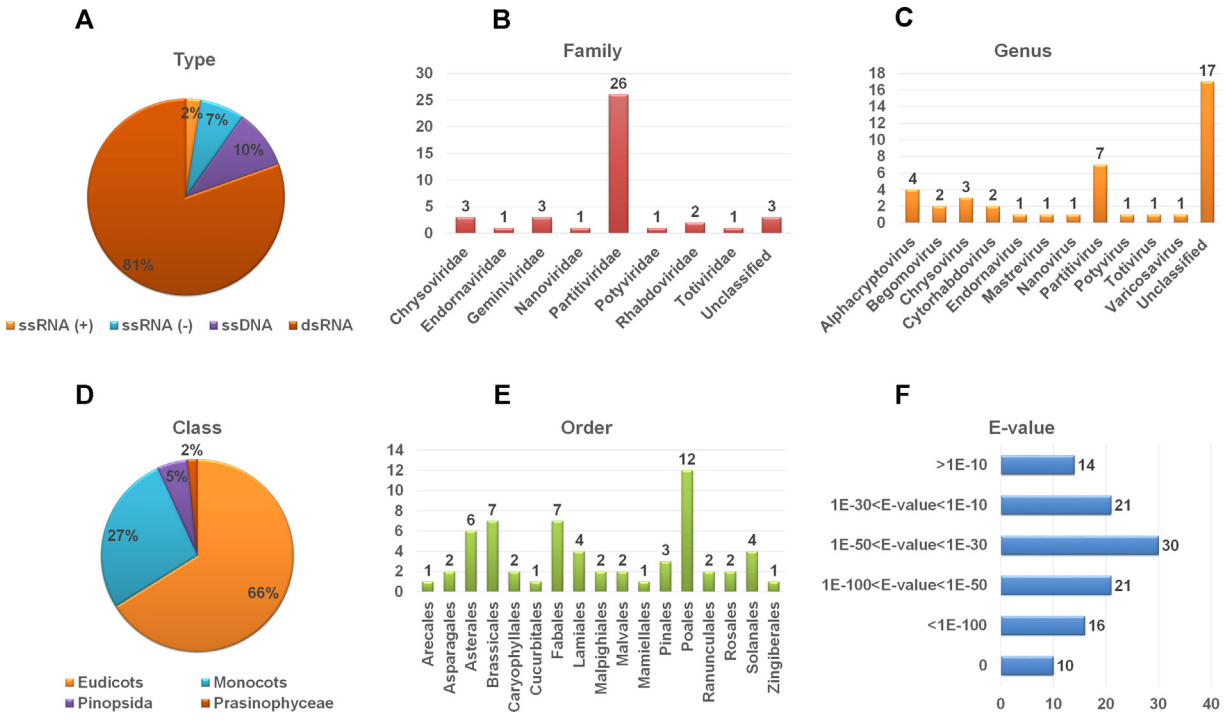

Fig. 2. Summary of identified ENREs integrated into plant genomes. Classification of identified ENREs according to virus type (A), family (B), genus (C), class (D), and order (E). Distribution of *E*-values of identified ENREs (F).

in *Arabidopsis thaliana*, *Brassica rapa*, *Brassica oleracea*, *Nicotiana tabacum*, *Zea mays*, and *Medicago truncatula*; and the related viral genes are predominantly the CPs of *Raphanus sativus cryptic virus* (RSCV) (1, 2, and 3), Rose cryptic virus 1 (RoCV), and *Fragaria chiloensis* cryptic virus (FCCV) [17]. Totivirus-like ENREs have been mostly identified from *M. truncatula*, *Lotus japonicas*, and *Populus trichocarpa* and have been matched to the CP of *Vicia* cryptic virus M, with the exception of CP-RDRP of Southern tomato virus isolate MS-7 [17].

Similarly, a recent study has identified many ENVRs matched to dsRNA viruses [10]. For example, the CP of a novel mycovirus infecting *Rosellinia necatrix*, referred to as RnPV2 CP and belonging to the family *Partitivirus*, showed a high level of similarity to ILR2, which has been reported as a homolog of SsPV-S CP [17]. Using available genome sequences for various plant species, an intensive blast search revealed that RnPV2 CP-like sequences are present in at least 17 plant species, such as *Arabidopsis*, *Capsella*, *Turritis*, *Olimarabidopsis*, and many members in the family Brassicaceae. The study identified a total of eight different partitivirus CP-like sequences (PCLS1 to PCLS8) derived from seven different dsRNA viruses, including RnPV2, RSCV1, RSCV2, RSCV3, FCCV, Carrot cryptic virus 1 (CaCV1), and RoCV [10]. Of these CPs, AtPCLS1 is already known as the ILR2 protein. In the case of PCLS2, three orthologous proteins have been identified from *Arabidopsis thaliana* (AT4G14104), *Manihot esculenta* (cassava4.1_029961m.g), and *Arabidopsis lyrata* (XM_002872767). Notably, PCLS2 is present in other *A. thaliana* accessions, such as Col-0, Ler, and Shokei, but not in other species, such as *A. lyrata*, *A. arenosa*, or *Capsella rubella*, which are all members of the family Brassicaceae, indicating that PCLS2 evolved differently than other members of the same family.

Another study identified novel dsRNA viral sequences in a publicly available expressed sequence tag (EST) database in silico [20]. A total of 119 novel virus-like sequences related to members of the families *Endornaviridae*, *Chrysoviridae*, *Partitiviridae*, and *Totiviridae* were subjected to a blast search. Similarly, RDRP-like and CP-like sequences derived from partitiviruses have been predominantly identified in various plants, including 10 monocot and 19 eudicot species. Interestingly, conifer plants such as *Picea* and *Psedutsuga* species also contain partitivirus-like sequences. Totiviral RDRP-like and CP-like sequences have been identified in *Phaeodactylum tricornutum* (diatom) and *Tamarix androssowii*, respectively. For chrysoviruses, RDRP-like and P3-like sequences were identified in *Artemisia annua* (sweet wormwood) and *Zinnia violacea* (garden zinnia), respectively. Additionally, 14 totivirus-like sequences were identified in various plants. Of these sequences, RDRP-like and CP-like sequences of Southern tomato virus (STV) were identified in seven plants, including *Festuca*, *Lolium*, *Triphysaria*, *Zingiber*, *Allium*, and *Brassica* species. Moreover, *Picea glauca* contains an endornaviral polyprotein-like sequence. A recent study demonstrated that Bell pepper endornavirus-like sequences homologous to the glycosyltransferase 28 domain are present in plants, fungi, and bacteria and that the glycosyltransferase 28 domain of Bell pepper endornavirus may have originated from bacteria [21]. Moreover, this study suggests the possible acquisition of glycome-related endornaviral genes from marine bacteria by HGT. Thus, extensive analyses are necessary to confirm the origin of these genes and the occurrence of HGT.

3.3. Integration of sequences derived from negative-strand RNA viruses into plant genomes

A recent study identified several negative-strand RNA viral sequences in various plants, including *P. trichocarpa*, *N. tabacum*, and *B. rapa* [10]. These sequences are homologous to the N proteins of members of the genus *Cytorhabdovirus*, such as Lettuce necrotic yellow virus (LNYV), Lettuce yellow mottle virus (LYMoV), and Northern cereal mosaic virus (NCMV) as well as CP proteins of members of the genus *Varicosavirus*, including Lettuce big-vein associated virus (LBVaV) [10]. Varicosaviruses with bipartite genomes are similar to cytorhabdoviruses with monopartite genomes [22,23]. Additionally, the N protein of rhabdovirus is similar to the CP protein of varicosavirus. Therefore, the negative strand

RNA viral-like sequences in the plant genome were named rhabdovirus N-like sequences (RNLSs), and at least four different RNLS proteins (RNLS1–RNLS4) have been identified [10]. In the case of RNLS1, homologous proteins have been identified in all test plants belonging to the genus *Brassica*. Interestingly, the RNLS2 protein has been only identified in *N. tabacum*, not in *N. benthamiana*.

3.4. Integration of sequences derived from plus-strand RNA viruses in plant genomes

A previous study revealed that potyviral-like sequences are present in the genomes of several grape varieties [16]. Southern and western blot analyses have found that the sequences homologous to the CP and 3′-UTR of *Potato virus Y* (PVY) are expressed in the grape genome [16]. A recent study identified sequences of 320 and 475 nucleotides in the *M. truncatula* database that are homologous to the CP and movement protein (MP), respectively, of *Cucumber mosaic virus* (CMV) [10]. However, these sequences have not amplified in *M. truncatula* line A17, which is used for genome sequencing. Additionally, a sequence related to the replicase polyprotein of the *Citrus leaf blotch virus* (CLBV), belonging to the family *Betaflexiviridae*, has been identified in the cucumber genome [10]. This protein was named *Cucumis sativus* flexivirus-like sequence 1 (CsFRLS1). PCR using specific primers for domains including methyltransferases, RNA helicases, and inter-domain regions has revealed the presence of such sequences in the cucumber genome but not in watermelon. In addition, a phylogenetic analysis has revealed that CsFRLS1 is similar to the genus *Citrivirus*.

3.5. Integration of sequences derived from single-strand DNA viruses in plant genomes

Three families of plant viruses have DNA genomes: the *Geminiviridae*, the *Circoviridae*, and the *Caulimoviridae*. Of these, the integration of DNA viruses into tobacco plants was first reported for the *Geminiviridae* viruses [15,24]. A study found that the multiple repeats of the replication initiation (Rep) sequence for the geminivirus were integrated into at least eight different tobacco cultivars [15]. Similarly, geminivirus-related DNA (GRD) sequences were identified in three related *Nicotiana* species but not in nine other, distantly related *Nicotiana* species, nor in other plants of the family Solanaceous indicating that all GRD elements were descended from a unique geminiviral integration event [25]. An extensive study found two GRD families; specifically, GRD3 and GRD5 on chromosomes 2 and 4, respectively, in which members were methylated and diverged [26]. A recent study using the representative Rep sequences of geminiviruses identified a geminiviral Rep-like sequence from *P. trichocarpa* and capsid protein-like sequences from *N. tabacum* [18]. Additionally, green algae, such as *Micromonas pusilla* CCMP1545, contain a geminiviral Rep-like sequence [18].

4. Functional roles of ENREs in plant genomes

After the integration of ENREs into the plant genome, their size is reduced via deletion and adaptation to host genomes over evolutionary time. A recent study clearly showed the pseudogenization, gene loss, and reduction in genome size of Tobacco etch virus (TEV) in *N. tabacum* by serial passage experiments [27,28]. There is research interest in identifying the potential roles of ENREs in host plants. Many studies suppose that ENREs in plants might confer viral resistance [14,29,30]. However, little is known regarding the possible roles of ENREs in virus resistance. A recent experimental study using transgenic tobacco plants expressing NIb of TEV showed that the expression of ENREs in plant genomes induces the deletion of the corresponding genes in viral genomes [28]. Of the known ENREs, *Arabidopsis* ILR2 has been shown to function in auxin conjugate metabolism and metal transport [31]. Additionally, it has been shown that the *Arabidopsis ilr2-1* mutant shows defects in lateral root formation and primary root elongation but is resistant to manganese- and cobalt-mediated inhibition of root elongation [31]. Given the association with virus resistance, we propose that the *ilr2-1* mutant is more susceptible than wild type *Arabidopsis* to virus infection. However, studies are needed to test our hypothesis.

5. Direction of horizontal gene transfer (HGT)

Gene transfer between a plant and virus can occur from host to virus or from virus to host. HGT from plant to virus has been reported for the Hsp70 gene, which was acquired from host plants by closteroviruses [32]. Additionally, mimiviruses have obtained several genes via HGT from hosts or bacteria [33]. Similarly, ENREs from endornaviruses might have acquired their glycome-related genes from marine bacteria by HGT. These findings support the hypothesis that HGT has occurred from host to virus. In contrast, most ENREs appear to have been transferred from virus to plant. For example, phylogenetic analysis has shown that plant PCLSs and partitivirus CPs are clustered together and that the viral sequences are basal in each major clade [10].

6. Concluding remarks

Only a limited number of ENREs have been identified to date. Interestingly, most identified ENREs are derived from dsRNA viruses, which infect fungi; this findings suggests possible HGT among plants, fungi, and viruses. The increasing availability of genomic data from viruses and host plants will enable the identification of additional ENREs in the near future. Following the identification of ENREs, the next step will be to characterize ENREs in plant genomes. Although some ENREs contribute only to the evolution of plant genomes, the expression of other ENREs might play important roles in host life cycles, such as defense against viral infection. Considered together, the ENREs identified to date provide insights into not only the co-evolution of viruses and plants but also the functional significance of ENREs in antiviral immunity.

Acknowledgments

We apologize to our colleagues whose work was not fully cited due to space limitations. This research was supported in part by grants from the National Research Foundation of Korea (NRF) grant funded by the Korea government (MEST) (No. 2011-0010027), the Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ009764) and the Next-Generation BioGreen 21 Program (No. PJ00798402) through the Rural Development Administration, Republic of Korea.

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