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Review

Analogies between geminivirus and oncovirus: Cell cycle regulation

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Geminiviruses are a large family of plant viruses whose genome is composed of one or two circular and single strand of DNA. They replicate in the cell nucleus being Rep protein, the only viral protein necessary for their replication process. Geminiviruses as same as animal DNA oncoviruses, like SV40, adenovirus and papillomavirus, use the host replication machinery to replicate their DNA. Consequently, they alter host cell cycle regulation to create a suitable environment for their replication. One of the events involved in this alteration would be the inactivation of the retinoblastoma protein (pRb) that negatively regulates the G1/S transition in cells. The discovery of one homologue of the pRb in plants and the finding that Rep protein of some geminiviruses interacts with human retinoblastoma protein, as well as animal virus oncoproteins, is very interesting. This finding laid the groundwork for subsequent detection of analogies between geminiviruses and animal DNA tumor viruses, especially in their interaction with pRb. Moreover, the finding allowed the determination of how this interaction affects the regulation of the cell cycle in plants and animals. Accumulated knowledge generates new interesting questions and possible implications, and so, in this document, we dare to watch in that direction.

Key words: Geminivirus, oncovirus, retinoblastoma protein, cell cycle regulation, endoreduplication.

INTRODUCTION

Geminiviruses are plant pathogens which have a single or double circular strand of DNA and replicates in the cell nucleus via a rolling circle mechanism (Bisaro, 1996). Due to the particularities of their replication, it has been found that geminiviruses are good candidates to act as models in studies of cell cycle regulation in plants (Gutierrez, 1999). The discovery of one homologue of retinoblastoma protein (pRb) in plants and the finding that Rep protein of geminivirus interacts with human pRb, as well as the oncoproteins of animal DNA tumor viruses like SV40, adenovirus and papillomavirus, suggest that geminiviruses could employ similar mechanisms to alter the host cell cycle regulation. We focused on the analogies between geminiviruses and animal DNA tumor viruses, especially in the interaction with pRb, and how this interaction affects the regulation of the cell cycle in plants and animals, as well as the questions and possible application derived from these interactions in both systems.

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Abbreviations: PCNA, Proliferating cell nuclear antigen; **WDV,** wheat dwarf geminivirus; **pRb,** retinoblastoma protein; **ACMV,** African cassava mosaic virus.

GEMINIVIRUSES

Geminiviruses, so called because of the “twinned” nature

of their particles, are a large and diverse family of plant viruses that infect a broad variety of plants and cause significant crop losses worldwide (Chasan, 1995; Hanley-Bowdoin et al., 1999). They belong to the family *Geminiviridae* and are classified into four genera according to their host range (monocots or dicots), insect vector (whitefly or leafhopper) and genome organization (monopartite or bipartite) (Yadava et al., 2010). The first genus, known as *Mastrevirus*, includes leafhoppers-transmitted viruses which have monopartite genomes and infect monocot plants. Maize streak virus is a type of species of this genus. The second genus, known as *Curtovirus*, includes geminiviruses with monopartite genomes that are transmitted to dicotyledonous plants by leafhopper vectors; while the last genus known as *Begomovirus,* is the largest and it houses the majority of the species in the family. Their members possess bipartite, or in a few cases, monopartite genomes are transmitted exclusively by whitefly vectors (*Bemisia tabaci*) and infect dicotyledonous plants (Brown, 2008; Briddon et al., 2010; Yadava et al., 2010).

Geminivirus genomes are small, consisting of either one or two circular ssDNA molecules ranging from 2.5 to 3 x 10^3 nucleotides in size. They have a small number of genes that are arranged in two divergent clusters separated by an intergenic region. In this region, all geminiviruses posses a GC-rich inverted repeat sequence that has the potential to form a stem-loop structure (Laufs et al., 1995).

Geminiviruses replicate to a high copy number and they contain a well-defined origin of replication. They encode only one protein essential for their replication (Rep protein) and recruit the rest of the replication machinery from their hosts (Hanley-Bowdoin et al., 1999; Yadava et al., 2010). Additionally, geminiviruses genomes are transcribed in a bidirectional manner resulting in mRNAs that correspond to both the virion and complementary-sense open reading frames (Gutierrez, 1999).

GEMINIVIRUS REPLICATION PROCESS

All geminiviruses employ the same general strategies to duplicate and express their genomes. Their replication and transcription are dependent on the nuclear DNA and RNA polymerases of the plant host. These properties are unusual among plant viruses, most of which are RNA viruses. Differing from RNA viruses which multiply in the cell cytoplasm and encode for their own replicases, geminiviruses multiply in the cell nucleus depending on the host replication enzymes (Hanley-Bowdoin et al., 2004). The overall strategy used by geminiviruses to replicate their ssDNA genome is similar to that of prokaryotic ssDNA phages and plasmids. Geminivirus replication proceeds through a rolling-circle mechanism which consists of two distinct stages: first, conversion of the genomic ssDNA into double-stranded DNA intermediates (a process carried out entirely by cellular factors) and secondly, the formation of new dsDNA intermediates and mature ssDNA genomes by a rolling-circle mechanism (Orozco and Hanley-Bowdoin, 1996; Castellano et al., 1999; Krupovic et al., 2009). Circular dsDNA forms are transcriptionally active templates, and their transcription occur bidirectionally depending on the activity of the two divergent promoters separated by a non-transcribed region where most of the *cis*-acting signals, regulating viral replication, are also located (Gutierrez, 2002).

All geminiviruses that are so far sequenced possess, in their intergenic region, a characteristic inverted complementary sequence, variable in composition and length, separated by an invariant 9-nt sequence (5'-TAATATTAC-3'). This sequence is present in the loop of the structurally conserved element and is shared by all geminiviruses. It is within this sequence that the initiation site for rolling-circle replication has been mapped (Fontes et al., 1994; Gutierrez, 2002). Besides this sequence, the intergenic region also contains iterated elements of around 8 to 12 nucleotides in length, which are specific binding sites of geminiviral replication-associated protein. This protein is called RepA and Rep in *Mastrevirus* and Rep in all geminiviruses (Argüello-Astorga et al., 1994; Hanley-Bowdoin et al., 2004).

Rep protein is encoded by all geminiviruses and is the only viral protein necessary for viral DNA replication. This protein has a sequence-specific DNA binding ability as well as site-specific endonucleolytic activity; so it catalyzes the initiation and termination of DNA synthesis (Gutierrez, 2002; Londoño et al., 2010). Most cells in mature plants have the capacity to dedifferentiate, resume cell division and form new plants. Differentiated plant cells normally require wounding or hormone application to reenter the cell cycle. It has been found that Rep protein induces expression and also interacts with the host proliferating cell nuclear antigen (PCNA), which is a factor for DNA polymerases during replication and repair, in non-dividing plant cells (Nagar et al., 1995; Castillo et al., 2003). This finding suggests that Rep protein can provide necessary stimulus to induce the dedifferentiation process. In addition, Kittelmann et al. (2009) found that expression of African cassava mosaic virus (ACMV) Rep protein in fission yeast (*Schizosaccharomyces pombe*) caused the cell elongation that resembles *cdc* (cell division cycle) phenotypes. Cells expressing Rep protein increased DNA contents, suggesting that ACMV Rep protein promotes reinitiation of nuclear DNA replication during the fission yeast cell cycle. They show that Rep protein, being the only viral factor, is sufficient to induce S-phase conditions in fission yeast. Xie et al. (1995), using the yeast two hybrid system, found that Rep protein of wheat dwarf geminivirus (WDV) contains retinoblastoma protein (pRb) binding motif (LxCxE) that is also present in the

oncoproteins of some animal DNA tumor viruses, and this motif is conserved in other geminiviruses.

GEMINIVIRUSES: THEIR INFLUENCE ON HOST CELL CYCLE REGULATION

In plants as in all eukaryotes, the four basic phases of the mitotic cell cycle (G1, S, G2 and M) are conserved. During their development, plant cells leave the cell division cycle, and in mature plants, DNA replication and the corresponding enzymes are confined to meristematic tissues (Oakenfull et al., 2002; Francis, 2007).

Geminiviruses replicate in differentiated cells where most of the cellular factors required for viral DNA replication are normally absent. Some geminiviruses are found in mature cells throughout leaves, stems and roots. These cells have left the cell division cycle and no longer contain detectable levels of plant DNA replication enzymes necessary for geminivirus replication (Gutierrez, 2002).

Due to the requirement for cellular factors, geminiviral DNA replication must be coupled to a special state of infected cell. This suggested that they might have evolved mechanisms which affected the expression of cellular genes involved in S-phase progression and G1/S transition (Gutierrez, 2000a; Hanley-Bowdoin et al., 2004). It has been found that geminivirus dsDNA replication intermediates are significantly more abundant in nuclei isolated from S-phase cells than in nuclei isolated from cells in other phases of cell cycle (Accotto et al., 1993; Hanley-Bowdoin et al., 2004).

One of the primary events involved in regulating this change of the host cell cycle seems to be the inactivation of the retinoblastoma protein (pRb) that negatively regulates G1/S transition in cells. Furthermore, this reliance on host enzymes and also the strategy used is similar to that seen during simian virus 40, human adenovirus, polyomavirus and papillomavirus replication in animal cells (Nagar et al., 1995; Gutierrez, 2002).

Studies on the ability of geminivirus proteins to interact with cell cycle regulatory pathways received significant attention. It is important to identify the events by which geminivirus takes advantage of cellular factors as well as in understanding the effects of geminivirus proteins on cellular gene expression, especially in genes involved in cell cycle regulation (Ach et al., 1997; Gutierrez, 2000b).

RETINOBLASTOMA PROTEIN: ITS ROLE IN CELL CYCLE REGULATION

In animal cells, the passage through G1 phase of cell cycle and transition from G1- to S-phase involves the activity of tumor-suppressor retinoblastoma protein (pRb) (Miskolczi et al., 2007). Rb tumor suppressor gene was the first tumor suppressor identified and it encodes a nuclear protein of 928 amino acids (110-kDa) (Weinberg, 1995; Zhu, 2005; Burkhart et al., 2010). It appears to function as a transcriptional cofactor that can repress or potentiate functions of many transcription factors, affecting the expression of a broad number of genes (Burkhart et al., 2010). Moreover, mutation of this gene was found in familial and sporadic retinoblastoma cases (Knudson, 1971).

Altogether, pRb, p107 and p130 belongs to the family of proteins that is known as “pocket proteins”, and this is due to the presence of a conserved domains in their C-terminal which are involved in the interactions of pRb with other proteins. This region includes highly conserved A and B domains and a distal C domain located at the C-terminus. Domains A and B constitute the “small pocket”, which has been identified in many studies as the minimal region required for pocket protein activity (Du and Pogoriler, 2006; Genovese et al., 2006; Sabelli and Larkins, 2009). To date, more than 100 pRb-interacting proteins have been identified, and between them is E2Fs, a family of transcription factors which play essential roles in the expression of many genes involved in S-phase and cell cycle progression. Association of these factors with pRb prevents transcription of genes required for cell cycle progression (Mittnacht, 2005; Du and Pogoriler, 2006).

pRb interaction with other proteins involved in cell cycle regulation is subject to regulation by phosphorylation. Also, it is phosphorylated in cells and the level of this modification change depends on the growth state and cell cycle progression. In the early G1 phase of the cell cycle, pRb is hypo-phosphorylated and interacts with E2F factors; but close to the late G1 phase and during the G1-S transition, pRb becomes phosphorylated by Cdk4/Cdk6 kinases in conjunction with D-type cyclins and loses its ability to interact with E2F factors (Mittnacht, 2005; Khidr and Chen, 2006; Miskolczi et al., 2007). E2F proteins regulate a broad spectrum of genes involved in cell cycle regulation, DNA damage response, apoptosis, differentiation and development, as well as other genes with unknown function (Zhu, 2005; Miskolczi et al., 2007). Moreover, all the known pRb-interacting proteins are preferentially bound to the hypo-phosphorylated form of the protein (Cam and Dynlacht, 2003; Miskolczi et al., 2007).

Sporadic somatic mutations in retinoblastoma (Rb) protein gene have also been identified in various cancers. This indicates that the tumor suppressor role of pRb is not restricted to the retina and its disruption is a general feature of cancer cells. In addition, it has been found that pRb, p107 and p130 proteins are all targeted by viral oncoproteins encoded by several small DNA viruses. These include the simian virus 40 (SV40) large T antigen, adenovirus EA1 and human papilloma virus E7 (Sabelli and Larkins, 2009). These viral proteins interact with the hypo-phosphorylated Rb and drive the quiescent cells into the cell division cycle (Lavia et al., 2003; Mittnacht, 2005).

Discovery of retinoblastoma (Rb) protein homologue and other components of the pRb pathway like E2F and D-type cyclins in plants (Grafi et al*.,* 1996; Ramírez-Parra et al*.,* 1999) suggests that, far from being restricted to the animal kingdom, at least some of the basic mechanisms which regulate cell cycle have been conserved throughout eukaryotic evolution (Jager and Murray, 1999; Heuvel and Dyson, 2008). These findings suggest that the basic pattern of controls that is operated during the G1 phase of the plant cell cycle is similar to that existing in animals (Oakenfull et al., 2002).

ONCOVIRUSES

The study of DNA tumor viruses in animal systems has facilitated the identification and functional analysis of key cellular pathways that are commonly dysfunctional during carcinogenesis in general (McLaughlin-Drubin and Munger, 2008). Study of these viruses began with the observation that they could reproducibly cause tumor formation in a variety of animals. It was found that SV40, a virus that contaminated rhesus monkey kidney cells used to prepare polio vaccine, could cause tumors in newborn hamsters and transform normal cells (Todaro et al., 1963; Coggin, 1969; Carbone et al., 1997). Similarly, human adenoviruses formed tumors when injected into newborn hamsters (Huebner et al., 1964; DeCaprio, 2009). These studies led to the search for specific mechanisms that enabled these viruses to cause tumors in the experimental model systems.

It has been found that mammalian DNA tumor viruses, similar to geminiviruses, rely on host replication enzymes in order to replicate their genetic material (Kong et al., 2000). One of the mechanisms employed by these tumor viruses to activate the host genes required for DNA replication is through binding of retinoblastoma protein, and relieving repression through E2F family of transcription factors (Levine, 2009).

Large T antigen from the simian virus 40 (SV40) can transform cells in culture and also induce tumors in rodents. In addition, some studies have found that T antigen from SV40, EA1 protein from adenovirus and E7 protein from papillomavirus interacts with retinoblastoma protein. As such, Rb protein specifically binds to shared motifs and domains in these oncoproteins. Conserved motif (LxCxE) of these proteins is a key factor in their interaction with pRb, while pocket domain of pRb is required for interaction with these viral oncoproteins (Levine, 2009; Sabelli and Larkins, 2009). In addition, this binding motif is found in plant D-type cyclins and in several replication-associated proteins (Rep) encoded by geminiviruses (Weinberg, 1995; Grafi et al., 1996; Shepherd et al., 2005).

Discovery of this motif and RepA proteins in Rep and in some geminiviruses and also the discovery of the interaction of these proteins with human pRb was the first clue, in which a similar mechanism could be used by geminiviruses in order to induce a suitable state of the host cell for their viral DNA replication. By modifying the plant cell cycle via Rep-pRb interactions, geminiviruses could provide a favorable environment for their replication (Torres-Pacheco et al., 1996; Kong et al., 2000; Kittelmann et al., 2009).

The cellular interactions between geminiviruses and their hosts related to the pRb pathway could be compared with that which occurred in animal DNA oncogenic viruses. More studies are needed to understand the correlation between interference with pRb pathway and geminivirus infection. One possibility is that geminiviruses induced a cell state in which the functions of S phase are over-regulated instead of originating an abnormal cell proliferation, causing a phenomenon known as endoreduplication. In fact, Ascencio-Ibáñez et al., (2008) found that three core cell cycle genes (CDKG1, CKL5 and CKL6), which are enhanced upon cell cycle reentry, had elevated transcripts in infected tissue of *Arabidopsis thaliana* plants infected with cabbage leaf curl virus (CaLCuV). This suggests that CaLCuV induces quiescent cells to reenter the cell division cycle. Moreover, they found that the level of genes expressed during G1 and M phase were primarily down, while S and G2 genes were up. The highest fraction of elevated transcripts was associated with S phase, while the greatest proportion of reduced RNAs was associated with M phase. This asymmetric expression patterns for cell cycle-association and the core cell cycle genes suggested that CaLCuV infection specifically activates S phase and inhibits M phase, resulting in the induction of endocycles (Ascencio-Ibañez et al, 2008). This indicates that geminiviruses can alter the host cell cycle by interacting with other factors, besides pRb, of the infected cell. On the other hand, there is the possibility that other pathways involved in tumor formation in animals by DNA oncoviruses exist in plants, but geminiviruses are not capable of altering and interacting with them.

ENDOREDUPLICATION

The normal cell cycle is characterized by a round of DNA replication followed by mitosis and cytokinesis, with both events separated by two gap phases (G1 and G2). In addition to the coupled cycles where S phase is followed by G2 and M resulting in two daughter cells, alternative cycles also occur in certain developmental situations, especially in plants. This phenomenon is called endoreduplication and it involves a repetition of S phases without an intervention of M phase and cytokinesis (Oakenfull et al., 2002; Inzè and Veylder, 2006). Also, it is a variant of the cell cycle in which cells stop dividing, although still growing and replicating (John and Qi, 2008). As was shown in the aforementioned, this could be an

effect of geminivirus infection (Ascencio-Ibañez et al, 2008).

In this cell cycle variant, cells amplified their genome without doing chromatin condensation, segregation and cytokinesis, resulting in multiple and uniform copies of nuclear DNA (Joubès and Chevalier, 2000). Endocycles are widespread in protists, plants and many animals including arthropods, mollusks and mammals. Some of the best examples include endosperm and nodule formation in plants, follicle in *Drosophila* and trophoblasts in rodents (MacAuley et al., 1998; Werner, 2007; Lee et al., 2009).

Observations have been made on endoreduplication as a consequence of mutations in genes controlling several aspects of the cell cycle regulation (Larkins et al., 2001; Lee et al., 2009). The specific physiological role of endoreduplication is still not known; however, several hypotheses have been proposed. One of them is that endoreduplication is essential to support cell growth and cell differentiation. Moreover, endoreduplication might be a mechanism to safeguard the genome that retains functional copies of important genes and also enhance the metabolic capacity of the plant (Inzè and Veylerd, 2006).

CONCLUDING REMARKS

Many of the fundamental control mechanisms that govern cell division in animals are also conserved in plants. The identification of genes involved in cell cycle regulation and DNA replication in plants would have a significant impact in plant cell cycle comprehension. Also, this would contribute to the understanding of some aspects of diseases that occur in animals, like cancer. On the other hand, geminiviruses are good models for the study of cell cycle and DNA replication; and this is due to their ability to alter cell cycle control in infected cell without tumor formation. Geminiviruses, similar to animal oncoviruses, depend on the host replication machinery to replicate their viral DNA; but in contrast with the latter whose infection causes abnormal cell proliferation and subsequent tumor formation, geminivirus infection does not cause these results in the plant. Therefore, the investigation of the reason why plants do not develop tumors when infected with geminivirus turns out interesting due to the existing similarities in the basic controls that operate during G1 phase of cell cycle in animals and also in the mechanism of oncovirus DNA replication process.

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