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RNA silencing pathways of plants: Silencing and its suppression by plant DNA viruses☆

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ABSTRACT

RNA silencing refers to processes that depend on small (s)RNAs to regulate the expression of eukaryotic genomes. In plants, these processes play critical roles in development, in responses to a wide array of stresses, in maintaining genome integrity and in defense against viral and bacterial pathogens. We provide here an updated view on the array of endogenous sRNA pathways, including microRNAs (miRNAs), discovered in the model plant Arabidopsis, which are also the basis for antiviral silencing. We emphasize the current knowledge as well as the recent advances made on understanding the defense and counter-defense strategies evolved in the arms race between plants and DNA viruses on both the nuclear and the cytoplasmic front. This article is part of a Special Issue entitled: MicroRNA's in viral gene regulation.

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1. Introduction

Like many other basic cellular processes, RNA silencing has initially been identified and studied in plants. In the 90s, while trying to generate transgenic plants over-expressing the chalcone synthase (CHS) gene, plant scientists made the critical observation that in most cases they obtained silenced plants instead of over-expressing ones [1,2]. Since then our knowledge on the trigger, spread and inheritance of RNA silencing has tremendously expanded and the different underlying molecular mechanisms have been deeply studied and are now well understood. In the present review, we present the basic endogenous mechanisms and the role of the silencing machinery in defense against DNA viruses.

2. The pathways of silencing in plants

Plants (and other organisms) use silencing for three purposes: 1) creating and maintaining heterochromatin of repetitive DNA and transposons, 2) regulating development, stress response and other endogenous regulatory functions and 3) defending against viral and bacterial infections. Although the arms race between host and pathogens certainly played a role in the diversification of RNA silencing mechanisms, it is not yet clear which of the different tasks were met first in evolution and which followed later.

The core of RNA silencing is the formation and recognition of double stranded (ds)RNA, which otherwise does not play a role in cellular genome replication and expression and which does not elicit an interferon response in plants. When recognized by DICER-LIKE (DCL) and dsRNA binding proteins (DRB), dsRNA is diced into 21–24 nt small RNA (sRNA) duplexes with 2-nt 3′-overhangs (see Ref. [3] for details). These duplexes interact with ARGONAUTE (AGO) and associated proteins to form RNA-induced silencing complexes (RISCs) with one of the sRNA strands in a process that is accompanied by the release/degradation of the other "passenger" strand.

RISCs are either involved in chromatin modification and then termed RNA-induced Transcriptional Silencing (RITS) complex, or in translation inhibition and cognate RNA degradation (slicing) depending on the AGO effector [4] and associated GW/WG motif containing proteins [5–7]. Cleavage products of the target RNAs are "aberrant" and can serve as template of RNA-dependent RNA-polymerases (RDR) to form dsRNAs, which again can initiate silencing in an autocatalytic, self-sustained manner. The enzymes involved in the silencing pathways are members of protein families, i.e. Arabidopsis has four DCLs, four DRBs, ten AGOs and six RDRs, specifically involved in different silencing pathways with partially-redundant functions. Plant DCLs differ in the size of the sRNAs they produce: DCL3 produces 24nt long sRNAs, DCL2 22nt ones and DCL4 21nt ones from long perfectly paired RNAs. DCL1 also produces 21 and 22 nucleotide long sRNAs but preferentially from short imperfectly paired hairpins. Next-generation sequencing data indicate that specific subsets of AGO

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proteins are connected to each DCL and that the stabilization of sRNAs into each AGO depends on preferential, hierarchical binding affinity of each AGO for the 5′ terminal nucleotide of the sRNAs [8,9]. AGO1 favors 21nt or 22nt 5′U-, AGO2 21nt 5′A-, AGO4 24nt 5′A- and AGO5 21-24nt 5′C-terminated sRNAs. AGO7 binds specifically to miR390 [8,10,11].

2.1. TGS pathways

Transcriptional gene silencing occurs in the nucleus and functions to initiate and maintain the heterochromatic state of certain DNA regions. Transcripts, which are probably considered aberrant, are produced from heterochromatin or DNA repeats by RNA polymerase IV (Pol IV) in a process that is sometimes preceded by the function of Pol II. These transcripts are transcribed by RDR2 into dsRNAs, which in Cajal body-like sub-domains within the nucleus, are diced by DCL3 into 24 nt long RNA duplexes with two-nucleotide 3′-overhangs. After methylation of the 2′-OH group by the dsRNA methytransferase HEN1, the passenger strand is discarded/degraded while the guide strand binds to AGO4 or sometimes to AGO6 or AGO9 depending on the loci and tissue [12–14]. It then forms together with scaffold transcripts made by Pol V [15], chromoproteins, histone H3K9 methylase (KYP) and DNA-methylating enzymes (Domain rearranged methylases [DRM2, DRM1] and Chromomethylase [CMT3]) a RNA-induced transcriptional silencing (RITS) complex involved in maintenance of histone- and DNA cytosine methylation (Fig. 1) [16].

It is not completely known what differenciates transcription by Pol IV from that by Pol II. Probably, Pol IV transcription occurs independently from standard promoters and enhancers, which would attract Pol II. Furthermore, Pol II transcription is connected to capping, splicing and polyadenylation, through molecular contacts of the relevant enzymes with the C-terminal domain (CTD) of Pol II [17]. Transcription events by Pol IV might however lead to transcripts lacking caps and/or polyA-tails like the aberrant transcripts, which are targets of RDRs.

Recently, long-miRNAs (lmiRNAs), 24-nt in length, were identified in Arabidopsis and then in rice and were shown to be produced from pri-miRNAs from exactly the same position as canonical miRNAs, but by the action of DCL3 [18,19]. Although the involvement of RDR2 and PolIV remains to be explained and the implication of the other proteins of the TGS pathway to be tested, two recent studies show that long miRNAs trigger the methylation of their targets and in some cases of their own genes [19,20]. The role of long-miRNAs is still elusive but given their strong expression in inflorescence tissues, one can speculate they act to silence *MIR* genes in meristematic cells and reproductive tissues.

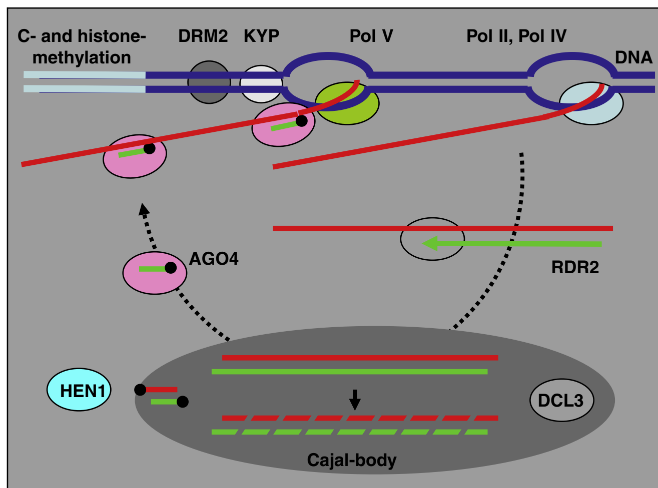

Fig. 1. Transcriptional gene silencing pathway. See Section 2 for details.

2.2. PTGS pathways

Three major silencing pathways are used to control host genes involved in various functions such as development and stress responses, the miRNA pathway, the ta-siRNA pathway and the nat-siRNA pathway (Fig. 2).

2.2.1. The miRNA pathway

Pri-miRNAs consist of a bulged hairpin flanked by unstructured arms. They are transcribed from the relevant *MIR* genes and are processed predominantly by the DCL1 “Drosha activity" and further by the DCL1 “Dicer activity”, yielding a miRNA duplex (see Ref. [3] for more details). With miRNA guide strand and AGO1 a RISC is formed, which binds to the cognate target and either slices it or arrests its translation.

Recent studies suggest that recently evolved *MIR* genes yielding longer hairpins are processed by the other DCLs to generate different size classes of siRNAs [18–21]. The *modus operandi* and biological significance of these siRNA species, which are just not sufficiently abundant to be annotated as miRNAs, remain to be determined.

2.2.2. The ta-siRNA pathway

TAS RNAs are transcribed from specific genes too, namely the *TAS* genes. Three families of these genes are known, the TAS1/2 family made of four members, the TAS 3 family made of three members and the TAS 4 family made of a single member [21–26]. TAS RNAs are originally capped and polyadenylated but become processed by DCL4 to generate secondary siRNAs—termed ta-siRNAs—upon cleavage guided by specific miRNAs (Table 1) [22–24,27–30]. These miR::AGO complexes are thought to recruit SGS3, which binds dsRNA with 5′-overhang [31,32] and RDR6 to convert TAS RNAs to the double-strand form (Fig. 2). It was shown that this secondary function of AGO1 depends on a 22nt miRNA, which can be generated from bulged precursors in contrast to 21nt one [33,34]. It is speculated that the larger miRNA size leads to a conformational change of AGO1, enabling it to fulfill this recruiting function [35]. For TAS3 as an alternative, a very specific AGO protein, AGO7 and targeting at two distant sites are required. The upper site is not sliced in contrast to the lower one, but from there the AGO7:miR390 complex serves to engage RDR6 (Fig. 3) [10,23].

The TAS RNA duplexes are diced by DCL4 and its cofactor DRB4 in phase into 21nt-, and at specific minor sites, 22nt-ta-siRNAs [29,36–38]. Ta-siRNAs are known to trigger themselves a cascade of siRNA biogenesis able to regulate several members of the same gene family [39]. Rajeswaran et al. [141] also show that following miR173 cleavage the entire polyadenylated parts of Arabidopsis TAS1a/b/c and TAS2 transcripts can be converted by RDR6 to dsRNAs. However, more abundant, shorter dsRNAs with one- or two-nucleotide 3′-overhangs are produced following a second cleavage directed by one specific ta-siRNA generated from TAS1c.

Ta-siRNAs generated from TAS1 and TAS2 mainly regulate the expression of pentatricopeptide mRNAs, those from TAS3 control auxin-response factor mRNAs to regulate abaxial–adaxial leaf polarity and phase change, and those from TAS4 regulate MYB transcription factor mRNAs to regulate anthocyanin biosynthesis in response to stress [30,37,39–43].

2.2.3. NAT-siRNA pathway

Nat-siRNAs are produced from overlapping dsRNA regions formed by natural antisense transcripts (NAT) and they define two classes: *cis*-nat-siRNAs, which arise from transcripts produced from the same genomic locus, and *trans*-nat-siRNAs, which arise from transcripts produced from physically distant genomic loci. C*is*-nat-siRNAs

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