Review

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RNAi and retroviruses: are they in RISC?

Abstract: RNA interference (RNAi) is a potent cellular system against viruses in various organisms. Although common traits are observed in plants, insects, and nematodes, the situation observed in mammals appears more complex. In mammalian somatic cells, RNAi is implicated in endonucleolytic cleavage mediated by artificially delivered small interfering RNAs (siRNAs) as well as in translation repression mediated by microRNAs (miRNAs). Because siRNAs and miRNAs recognize viral mRNAs, RNAi inherently limits virus production and participates in antiviral defense. However, several observations made in the cases of hepatitis C virus and retroviruses (including the human immunodeficiency virus and the primate foamy virus) bring evidence that this relationship is much more complex and that certain components of the RNAi effector complex [called the RNA-induced silencing complex (RISC)], such as AGO2, are also required for viral replication. Here, we summarize recent discoveries that have revealed this dual implication in virus biology. We further discuss their potential implications for the functions of RNAi-related proteins, with special emphasis on retrotransposition and genome stability.

Keywords: Argonaute; AGO2; foamy virus; hepatitis C virus (HCV); human immunodeficiency virus type 1 (HIV-1); microRNAs; retrovirus; virus.

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Introduction

RNA interference (RNAi or RNA silencing) is at the core of potent defense systems against invading nucleic acids, including transposable elements and exogenous viruses. The underlying molecular mechanisms are disparate among species and cell types and range from transcriptional gene silencing to post-transcriptional RNA degradation and translation inhibition (1–8). A common trait of these antiviral mechanisms is the recognition of viral nucleic acids by 20- to 30-nt noncoding RNAs (ncRNAs), which gives the RNAi machinery its specificity (4, 9–14). The ancestral RNAi machinery is thought to comprise one Dicer-like RNase III, one Argonaute (AGO) protein, one P-element-induced wimpy testis (PIWI) protein as well as one RNA-dependent RNA polymerase (15–17). The latter is only present in certain eukaryotes (15), where it is implicated in RNAi propagation and amplification (18). Interestingly, the greatest conservation among these polypeptides is found in AGO-PIWI proteins (15), which are invariably present in all species where RNAi has been documented. Specific species independently lost either one or the other class of proteins, and only animals appear to have retained both (15–17). For instance, the human genome encodes four PIWI (PIWI-like 1–4, or PIWIL1–4) and four AGO proteins (AGO1–4) (16, 19). The 20- to 30-nt ncRNAs are often, if not invariably, processed from double-stranded RNAs by Dicer-like and/or AGO-PIWI-like proteins (9). The ncRNAs are then loaded onto members of the AGO-PIWI effectors, which represent core proteins of the RNAi effector complex RISC (RNA-induced silencing complex).

Antiviral RNAi in mammals

The first discovered natural function of RNAi was the antiviral response in plants, wherein the replication of RNA and DNA viruses is associated with a massive generation of virus-derived small RNAs by cellular Dicers (1, 5, 20). These small RNAs further trigger the cleavage of viral messengers, thereby limiting viral infection. A similar type of

defense is observed in insects and nematodes (1, 6, 20). In mammals, although artifically induced RNAi is clearly potent against various viruses (21), viral infections do not seem to be associated with a massive production of virus-derived small ncRNAs (7, 22–24). The mammalian antiviral RNAi rather seems to rely on small ncRNAs derived from cellular RNAs. In mammals, at least three classes of small ncRNAs have been identified (9, 14): endogenous small interfering RNAs (endo-siRNAs), PIWI-interacting RNAs (piRNAs), and microRNAs (miRNAs). To date, a well-characterized function of endo-siRNAs and piRNAs is the maintenance of genomic integrity by silencing of transposable elements in germline cells (2, 3, 9, 25). Accordingly, mammalian endo-siRNAs are highly expressed in oocytes (26) and embryonic stem cells (27, 28), and piRNAs have consistently been reported to be essentially expressed in male and female germline cells (2, 3). The third class, miRNAs, recognizes mRNA targets through imperfect homologies and induces an AGO-based translation repression, which is associated with mRNA deadenylation and degradation (12, 29–31). The RISC complex, miRNAs, and targeted mRNAs are found in particular cytoplasmic foci, called processing (P) bodies (32). Although some differences may exist (33, 34), the four human AGO proteins bind to miRNAs and play redundant functions in translation control (35).

Thus far, given our current knowledge, miRNA is the major class of ncRNAs faced by exogenous viruses in mammalian somatic cells. There is over a thousand miRNAs in the human genome (1600 precursors and 2042 mature in miRBase v19) that can be predicted to modulate more than 50% of human protein-coding genes (36), and miRNAs have been shown to play a role in most if not all cellular processes. Three classes of miRNA-virus interactions can easily be distinguished. First, several viruses encode their own miRNAs to regulate viral and/or cellular mRNAs (37). Although the capacity of herpesviruses, adenoviruses, and polyomaviruses to generate such viral miRNAs is unequivocal (37), several studies have also provided evidence of the existence discrete species of small ncRNA, akin to viral miRNAs, for other types of viruses (38–42). Second, viruses specifically modulate the host miRNA repertoire, and these modulations can create favorable conditions for viral replication (43–47). Some viruses also widely affect the host miRNA repertoire by directly interfering with the miRNA biogenesis machinery. For instance, human immunodeficiency virus type 1 (HIV-1) suppresses the expression of Dicer *via* the viral gene *Vpr* in macrophages (48). In addition, HIV-1 (39, 48) and HTLV-I (49) inhibit the action of Dicer. In fact, it is now admitted that, similar to the situation observed in plants and insects (1), viruses produce proteins and/or RNAs that can negatively interfere with various steps of RNAi [reviewed in (50)]. Third, host miRNAs can recognize viral mRNAs (51–62). This process is thought to be similar to that described for endogenous miRNAs. It tethers the RNAi machinery, in particular AGO2, to viral messengers and leads to the sequestration of viral RNAs in P bodies and the inhibition of their translation (58, 63). Therefore, host miRNAs may have a potential as an RNA-based antiviral system (51, 54–62, 64). In fact, this particular interplay is exploited in genetic engineering and therapeutic gene transfer to artificially regulate transgene expression (61, 65, 66). However, several findings bring evidence that the relationship between RNAi and viruses in mammalian somatic cells is much more complex. Notably, viruses seem to have co-evolved with the miRNA repertoire of their hosts (67, 68), and some viruses have been reported to be able to exploit the miRNA recognition during the course of their replication (53, 56).

AGO2 and hepatitis C virus

Soon after the observation that a cellular miRNA recognizes the RNAs of primate foamy virus type 1 (PFV-1) and limits viral replication (51), Jopling et al. (53) reported that the liver-specific miR-122 recognizes hepatitis C virus (HCV) RNAs and that this recognition is beneficial for HCV replication. This decisive paper provided the first evidence that the interplay between viral RNAs and cellular miRNAs is more complex than previously thought and opened new avenue for the development of original miRNA-based therapy [reviewed in (69)]. Indeed, the treatment of chronically HCV-infected chimpanzees with the locked nucleic acid-modified antisense oligonucleotide miravirsen directed against miR-122 leads to a long lasting suppression of HCV viremia with no evidence of viral resistance or side effects in the treated animals (70), and in 2010, Santaris Pharma initiated a phase IIa study to assess the safety and antiviral activity of miravirsen in treatment-naive HCV patients (71). That study shows that miravirsen given as a 4-week monotherapy treatment provided robust, dose-dependent antiviral activity with a mean reduction of 2 to 3 logs from baseline in HCV RNA (log10 IU/ml) that was maintained for more than 4 weeks beyond the end of therapy and that in four of nine patients treated with the highest doses of miravirsen, HCV RNAs became undetectable during the study (71).

At the cellular level, miR-122 binds two sites in the 5′ untranslated region of HCV mRNAs to promote viral

replication (52, 53). miRNAs usually interact with the 3′ end of target mRNA to downregulate their expression. Accordingly, introduction of an miR-122 target site in the 3′ noncoding region of HCV genomic RNA leads to an miR-122-dependent downregulation of its expression (52). The location of the miR-122 binding site thus appears to dictate its effect on the genomic RNA. This is likely not limited to miR-122 because similar observations have been made on the regulation of endogenous mRNA by miR-10a (72). Although it is clear that miR-122 contributes positively to HCV replication, the molecular mechanisms are still only partially understood. miR-122 is able to stimulate HCV translation (73–77), but this effect is not sufficient to fully explain its actions on HCV replication (76). Recently, miR-122 was shown to promote the accumulation of the viral genome (77, 78) by protecting it from the host mRNA decay machinery (78). This stabilization of HCV RNA by miR-122 could also be in part responsible for the observed miR-122-induced enhancement of HCV translation (78). In both cases, AGO2 is required for the effect of miR-122 on HCV (75, 77, 78). Importantly, HCV does not hijack the whole RNAi machinery but only some components, in particular AGO2. This is supported by observations that HCV RNA-miR-122 complex reroutes some but not all components of the RNAi machinery to replication foci that are distinct from P bodies (79, 80). In fact, P-body disruption does not alter virus protein levels and virus production (80). Conversely, the HCV RNAs interact with P bodies when cleaved by artificially delivered siRNAs (79). Together, these results unveil a new function for AGO2 in HCV replication, which (i) is mediated by the miR-122, (ii) probably occurs in a subcellular structures distinct from P bodies, and (iii) is beneficial for the virus. Interestingly, interferon β, which is used in standard treatments against HCV, increases the expression of several cellular miRNAs interfering with HCV replication while it decreases the expression of the miR-122 (55). The balance between the two functions of AGO2 is thus likely to influence the outcome of HCV infection.

AGO2 and retroviruses

We have recently unveiled a dual interaction of AGO2 with retroviral RNAs (81). We showed that both the wild-type AGO2 protein and the well-characterized PAZ9 mutant that lost the ability to bind miRNAs (82) were able to interact with the retroviral GAG core proteins of both HIV-1 and PFV-1. As a consequence, AGO2 was found to be tethered to unspliced retroviral RNAs that are bound to GAG through their encapsidation sequences. We also showed that this GAG-dependent but miRNA-independent binding did not elicit retroviral mRNA translational repression (81). In addition, AGO2 depletion was shown to be detrimental to retroviral replication in human somatic cells (81). Hence, there are at least two ways to recruit AGO2 on retroviral mRNAs: one elicited by host miRNAs and negative for viral replication (51, 56–58, 63); second, mediated by GAG and the RNA packaging sequences, implicated in retroviral particle formation (81). These two types of interaction, which are not exclusive and are likely involved in distinct steps of the retroviral life cycle, are reminiscent of the dual interaction of AGO2 with HCV. The recognition of viral mRNAs by cellular miRNAs (51, 57, 58, 63, 83) and their sequestration in P bodies (58, 63) might thus represent the deleterious consequences of the recruitment of AGO2 or other RNAi-related components in viral replication. The mechanism by which AGO2 plays a positive role on retroviral replication is still poorly understood. Using FRET/FLIM experiments, we showed that AGO2 is required for PFV-1 GAG multimerization (unpublished data). This observation, which is consistent with the role of AGO2 in retroviral particle formation, is supported by electron microscopy observations showing an accumulation of HIV particles with an immature morphology in infected cells knocked down for AGO2 (81). In line with these results, Reed et al. (84) have shown that during the assembly of immature capsids, HIV-1 GAG traffics through a pathway of assembly intermediates that contain endogenous P-body-related proteins, including AGO2 and the RNA helicase DDX6 (also called p54/RCK). DDX6 was further shown to facilitate GAG multimerization at the plasma membrane and capsid assembly independent of RNA packaging (84). The authors proposed that HIV-1 assembly co-opts a pre-existing host complex containing cellular facilitators such as a particular P-body-related protein that the virus uses to catalyze capsid assembly (84). Together, these studies reveal that AGO2 and presumably other RNAi-related proteins play central and positive roles in the assembly of retroviral particles.

Expert opinion: dual actions of RISC components in retroviral replication

We have performed RNAi experiments against several RNAi-related proteins, and we have observed that while AGO2 RNAi consistently diminished both HIV-1 and PFV-1 replication, RNAi directed against other AGOs, GW182, and DDX6 yielded great standard deviations and inconclusive

results regarding their contribution in retroviral replication (81). However, several independent studies have shown that DDX6 is required for PFV-1 (85), HCV (86, 87), and HIV-1 (84) replication. This is in contrast with three other papers that reported that DDX6 either has no effect (88) or limits HIV-1 replication (58, 63). In fact, contradictory results have often been observed knocking down different RNAi-related components (Table 1). For instance, Dicer was shown to be required for HIV-1 replication (89), whereas another study (47) reported that it is detrimental. The Moloney leukemia virus 10 (MOV10) protein, which interacts with AGO2 (90–92), has been reported to be either beneficial (93) or deleterious (94, 95) for HIV-1 replication. Interestingly, MOV10 is widely implicated in the replication of various retroviruses, even retroelements. Wang et al. (95) have reported that MOV10 reduces the infectivity not only of HIV-1 but also of simian immunodeficiency virus and murine leukemia virus. Endogenous MOV10 also inhibits retrotransposition of intracisternal A particles (IAPs) (96) as well as that of other LTR and non-LTR endogenous retroelements (97). Strikingly, in contrast to Wang et al. (95), Arjan-Odedra et al. (97) reported that depletion of endogenous MOV10 had no significant effect on the production of infectious particles for a panel of exogenous retroviruses (HIV-1, SIVmac, MLV, or M-PMV). Hence, at present, it is difficult to conclude on a general effect of the RNAi machinery on viral replication. It is likely that the ability of RNAi-related proteins to inhibit and/or promote viral replication depends on their interacting partners. In fact, the exact composition of the RNAi machinery is still not fully defined, and it is likely to vary in time and in specific cells. Thus, the accumulation of data is clearly required before drawing any definitive conclusion. For instance, a better characterization of AGO2 domains implicated in viral replication as well as proteomics approaches aimed at determining the dynamic composition of the AGO2 and GAG containing complexes (90–92, 98) may provide invaluable information. Likewise, a better characterization of AGO2-regulating proteins (99), AGO2 post-translational modifications (100, 101) and/or particular subcellular localizations (102, 103) could also profoundly impact our understanding of the complex interplay between the RNAi machinery and viruses.

Outlook

RNAi and retrotransposition

Because HIV-1 and PFV-1 are among the most distant retroviruses (104–106), features common to these two viruses are likely to be conserved in the whole Retroviridae family including endogenous retroviruses and retrotransposons. In fact, foamy viruses can be found in endogenous forms (107, 108). Moreover, PFV-1 exhibits the unique property among exogenous retroviruses to retrotranspose (109),

Table 1 The yin and yang of RNAi proteins: examples of RISC-associated proteins having dual actions in virus biology.

AGO2	Inhibits	Viruses through therapeutic RNAi [reviewed in (21)]
	Is required	PFV-1 (81)
		HIV (81)
		HCV (75, 77, 80)
p54/RCK (DDX6)	Inhibits	Viruses through therapeutic RNAi [reviewed in (21)]
		HIV-1 (58, 63)
	Is required for	PFV-1 (85)
		HCV (86, 87)
		HIV-1 (84)
	Has no effect on	HIV-1 (88)
Dicer	Inhibits	Viruses through therapeutic RNAi [reviewed in (21)]
		HIV-1 (47)
	Is required for	HIV-1 (89)
MOV10	Is required for	HIV-1 (93
	Inhibits	Viruses through therapeutic RNAi [reviewed in (21)]
		HIV-1 (94, 95)
		Simian immunodeficiency virus (95)
		Murine leukemia virus (95)
		Intracisternal A particles (96)
		LTR and non-LTR retroelements (97)
	Has no effect on	HIV-1, SIVmac, MLV, and M-PMV (97)

and this retrotransposition depends on the expression of a functional GAG protein (109). As AGO2 affects PFV-1 replication (81), presumably at or before the GAG multimerization step (unpublished data), it may also influence PFV-1 retrotransposition. Strikingly, PFV-1 GAG shares several features with the GAG protein of the *Saccharomyces cerevisiae* Ty1 retrotransposon, which bring it closer to this retrotransposon than to HIV-1 (106, 110, 111). Ty1 virus-like particle (VLP) assembly requires some P-body proteins but not P-body foci *per se* (112). Likewise, the VLPs of Ty3 retrotransposon assemble in association with P-body components (113). In human cells, the RNA-binding protein ORF1 of the LINE-1 retrotransposon localizes with AGO2 and can physically interact with several of its partners (114). These interactions have been proposed to mitigate the potential mutagenic effects of retrotransposition by sequestering LINE-1 ribonucleoproteins and possibly targeting them for degradation (114), a scenario similar to that described for IAPs (115) and exogenous retroviruses (51, 58, 63). Meanwhile, given that some components of the RNAi machinery have a dual role on the life cycle of exogenous retrovirus, it would be also worth investigating whether AGO2 and some of its partners can positively regulate LINE-1 ribonucleoprotein formation and retrotransposition.

Likewise, it might be of interest to evaluate whether endogenous retroviruses exhibit relationships with the PIWI proteins comparable to that reported for AGOs and exogenous retroviruses (81, 84). Endogenous retroviruses are present in both somatic and germinal cells and therefore face both AGO and PIWI proteins, in contrast to exogenous retroviruses, which can only interact with AGO proteins in somatic cells. The particular case of endogenizing retroviruses (108, 116–119) might also provide an exciting homogeneous framework to study the interplay existing between exogenous/endogenous retroviruses and AGOs/PIWIs.

Viruses to probe unconventional functions of the RNAi machinery

A body of evidence suggests that RNAi proteins, such as AGO2, have functions that are different from the classical RNAi pathway. First, RNAi proteins function independently from miRNAs. For instance, the *S. cerevisiae* genome does not encode miRNAs but contains several homologues of RNAi proteins (15). Also, mouse and human AGO2-mRNA interactions can take place in the absence of miRNAs (81, 98). Second, AGO2 has functions that are distinct from translational control such as transcriptional gene silencing (120) and DNA double-strand break (DSB) repair (121). Transcriptional gene silencing depends on the recruitment in the nucleus of miRNAs onto the promoter region of the gene that is silenced (120). Meanwhile, DSB repair requires specific 21-nt DSB-induced small RNAs that are distinct from miRNAs and represent a new population of ncRNAs that needs to be further characterized (121). Finally, RNAi proteins can be found in specific subcellular locations and protein complexes that are not linked to miRNA biogenesis or RNAi (92, 102). Together, these observations indicate that in mammalian somatic cells, certain components of the RNAi machinery play additional functions independently from miRNAs and translation control that remain to be properly characterized. AGO2 mutations and/or dysregulations have been observed in certain malignancies, in particular cancers (122–124). In breast cancer, the expression of AGO2, as opposed to other AGOs, correlates with tumor subtypes (125). One may legitimately anticipate that AGO2 deregulation is linked to carcinogenesis by leading to global changes in miRNA expression/action. However, while AGO2 and AGO1 play redundant functions in miRNA-mediated translation repression, forced expression of AGO2 in breast cancer cell lines enhances proliferation, reduces cell-cell adhesion, and increases migratory ability (124). In contrast, AGO1 acts as a tumor suppressor gene (126). Hence, the sole action of AGOs in miRNA-mediated translation repression cannot explain these contrasting results. We may then assume that AGO2 deregulations impact other cellular pathways independently of miRNAs. Notably, as discussed above, AGO2 and other components of the RNAi machinery could help retransposons such as LINE-1 to form active ribonucleoparticles. The retrotransposition of LINE elements has indeed been implicated in natural human genome mutagenesis (127–133), and several other retroelements remain active in our genome (134). It is possible that the increased AGO2 expression observed in certain cancers (123–125) will favor ribonucleoparticle assembly and retrotransposition, thereby contributing to retrotransposon-triggered mutagenesis. We therefore contend that a better characterization of the complex interplay between (retro)viruses and the RNAi machinery will unveil unanticipated results that may impact unsuspected aspects of cell biology.

Highlights

- RNAi and miRNAs can limit viral replication.
- Viruses, including HCV and retroviruses, hijack some components of the RNAi pathway to facilitate their replication.

- RNAi proteins play dual functions in viral life cycle, making it difficult to draw definite conclusions regarding the overall effects of the RNAi machinery on viral replication.
- A better characterization of the protein complexes involved is clearly required.
- This characterization may reveal unsuspected functions of the RNAi-related proteins.
- AGO2 mutations and/or dysregulations have been observed in certain malignancies, in particular, cancers.
- It would be worth investigating whether RNAi-related proteins, including AGO2, positively regulate retrotransposition.
- AGO2 roles in retroviral particle formation may shed a new light on retrotransposon-triggered mutagenesis.

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