Viral miRNA production in human adenovirus serotype Ad4, Ad5, Ad11, Ad12, and Ad37 infections.

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Micro RNAs (miRNAs) and small interfering RNAs (siRNAs) are the two large classes of small regulatory RNAs generated by enzymatic cleavage of double stranded RNAs (dsRNAs). They down regulate gene expression by binding to their target mRNAs in a homology dependent manner. This dsRNA dependent sequence specific eukaryotic gene silencing mechanism is known as RNA interference (RNAi) for which Fire and Mello shared the Nobel Prize in physiology or medicine in 2006.

Many viruses produce dsRNA upon infection, which, in turn, stimulate RNAi in host cell to mediate an anti-viral response through viral mRNA degradation. To overcome this host defense, viruses are able to adopt different strategies. It has been reported that many viruses use proteins or RNAs to suppress the RNAi pathway of the host anti-viral defense. Human adenovirus type 5 (Ad5), for example, encodes two virus-associated RNAs (VARNAI and VARNAII) that are found to be critical in mediating the suppression of the RNAi host response by interacting with two key RNAi pathway enzymes, Dicer and RNA Induced Silencing Complex (RISC). VARNAs compete for Dicer cleavage thus generating viral miRNAs, so called mivaRNAs. Acting as the competitive substrate against cellular small regulatory RNAs, these mivaRNAs incorporated into RISC and thus down regulate RNAi induced viral mRNAs.

More than 50 human adenovirus serotypes have been classified into seven subgroups. Although the suppression of the RNAi host defense by Ad5 has been studied extensively, it is yet unclear whether this mechanism is common for all serotypes. To puzzle out this we studied Ad4, Ad11, Ad12 and Ad37 from different subgroups. Our experiment showed that all these serotypes produce mivaRNAs that incorporated into RISC efficiently, indicating that all the serotypes tested share a common RNAi suppression mechanism. Our findings also suggest differences in mivaRNA cleavage efficiency, RISC incorporation and expression levels from serotype to serotype, with Ad37 showing the highest mivaRNA expression and the highest efficiency in host cell protein synthesis inhibition during lytic infection.

Researchers became highly interested in the use of the adenovirus in such medical applications as gene therapy or vaccination due to its comparatively less severe infectious property. Understanding of adenovirus-host interaction attempted in this study, is, therefore, crucial to develop a safe adenoviral therapy. Further research is required to understand the role of mivaRNA-RISC complex and the reasons behind functional redundancy of VARNA in adenovirus infections.

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