Modeling and Optimization of the Interaction between RNA Silencing Pathway and Viral Suppressors of Silencing

Guillermo Rodrigo[1], Javier Carrera[1], Alfonso Jaramillo[2], and Santiago F. Elena[1]

[1] Instituto de Biología Molecular y Celular de Plantas, CSIC-UPV, Ingeniero Fausto Elio s/n, 46022 Valencia, Spain
[2] Laboratoire de Biochimie, CNRS UMR-7654, École Polytechnique, Route de Saclay, 91128 Palaiseau, France

The underlying working principle in RNA silencing relies on the auto-repressive action triggered by the intracellular presence of double-stranded RNA (dsRNA). RNA-dependent RNA polymerases (RdRp) replicate single-stranded RNA (ssRNA). This ssRNA can be aberrant or external (from viruses or viroids). During replication, dsRNA intermediates are formed and a cellular molecule, called DICER, degrades these dsRNA into 21 to 24 units called small interfering RNAs (siRNA). Subsequently, the cellular RNA-induced silencing complex (RISC) loads these small RNAs resulting in the active form RISC*. Then, the sequence complementarity between the loaded siRNA and the viral genomic RNA guides RISC*, resulting in the cleavage of the target RNA. Furthermore, in a secondary cycle of amplification, the siRNAs can be used as primers to generate more siRNAs. siRNAs can be moved from cell-to-cell immunizing new cells against infection. Given the properties of the RNA silencing pathway (specificity and amplification), it represents a sort of immune system in plants.

However, viruses have evolved strategies to escape for silencing surveillance while promoting their own replication. Several viruses encode suppressor proteins which interact with elements of the silencing pathway and block it. Several possible viral strategies exist, depending upon which is the target of the suppressor: DICER, siRNA, RISC, or cell-to-cell diffusion of siRNAs. Also,, the viroids also can escape from RNA silencing by means of their highly folded structure.

Here, we present a mathematical study of the silencing mechanism and develop models that incorporate different suppressor activities. These models are very important to unveil defense strategies and design principles of genetic systems. In addition, we have performed a parametrical optimization of this pathway to explore in which regions of parameter space hosts can evolve optimal strategies able of silencing different viruses and also whetherviruses can evolve capable of surviving in different hosts.