Studies on plant viruses and host antiviral resistance with a combined approach of molecular biology and mathematical modeling

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Abstract

Viruses rapidly adapt to changes in environments. This often leads to our failure in controlling viruses in crop fields due to rapid emergence of viral variants that overcome the resistance that were introduced into crop plants. Error-prone replication of viruses stochastically provides more adaptive variants to given environments (e.g., resistance-overcoming variants) at certain probabilities, as well as defective ones at significantly higher probabilities. Because viruses replicate and accumulate in host cells, viral gene products are shared among each intracellular viral population, which accumulates up to 10 million copies. The shared use of gene products allows defective variants to make use of the intact gene products from others; it also prevents more adaptive variants from enjoying the merit of their variations. Thus, this is potentially a serious problem for viruses to achieve rapid adaptation and to maintain their genomes. Our experiments showed that several plant RNA viruses commonly infect a host cell at MOI smaller than 6 after cell-to-cell movements, and a plant DNA virus infects a cell at MOI smaller than 3. Our simulation showed that such small MOIs in cell infections enable rapid selection by stochastically separating the adaptive and defective variants (1, 2). Currently we are trying to develop new measures to control viruses that target the share use of gene products among intracellular viral populations – the "Achilles' heel" of viruses found in our studies.

In addition to the above studies, I have been studying NLR-mediated antiviral resistance of land plants since I joined Hideki Takahashi's lab at Tohoku University. Genomes of land plants carry tens to hundreds copies of *NLR* genes, and their gene products, NLR (NB-LRR receptor) proteins, function as sensors to pathogen infections to induce resistance. In many cases, each NLR recognizes a specific protein of a pathogen. For instance, RCY1, an NLR of *Arabidopsis thaliana*, recognizes the coat protein (CP) of cucumber mosaic virus (CMV) to induce typical hypersensitive response (HR), which is characterized by inhibition of systemic infection of the virus and formation of necrotic local lesions via induction of programmed-cell death. It is often considered that cell death in HR inhibits systemic viral infection; however, there are many studies that showed that induction of the cell death is not necessary or sufficient for inhibition of systemic infection of the viruses. We showed that MOI of CMV in the first and second cell-to-cell infections decreased by ~30% upon HR induction; such MOI reduction occurred prior to cell death induction, implying that cell death is induced in a post-hoc manner in the cells that accumulated a certain amount of the virus. We also showed that inefficient NLR-mediated resistance induction against a CMV variant caused systemic infection of the virus and post-hoc systemic death of the infected plant individuals, which is called systemic HR or SHR. Our simulation showed that such individual death can function as an antiviral population resistance mechanism by reducing the infection source to neighbor kin plants, considering that land plants form clusters of genetically close individuals. This idea nicely explained the benefit of post-hoc cell death induction in HR and SHR, as well as the dramatic increase in the number of *NLR* genes in the history of land plants evolution (3).

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