

Viewpoint

Diverse plant viruses: a toolbox for dissection of cellular pathways

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Research in virology has usually focused on one selected host–virus pathosystem to examine the mechanisms underlying a particular disease. However, as exemplified by the mechanistically versatile suppression of antiviral RNA silencing by plant viruses, there may be functionally convergent evolution. Assuming this is a widespread feature, we propose that effector proteins from diverse plant viruses can be a powerful resource for discovering new regulatory mechanisms of distinct cellular pathways. The efficiency of this approach will depend on how deeply and widely the studied pathway is integrated into viral infections. Beyond this, comparative studies using broad virus diversity should increase our global understanding of plant–virus interactions.

Viruses represent the most numerous and diverse organismal group defined to date (Culley *et al.*, 2007; Paez-Espino *et al.*, 2017) and there are multiple hypotheses speculating that viruses contributed to the origin of cellular life and have a longstanding co-evolutionary history with higher life forms (Durzyńska and Goździcka-Józefiak, 2015; Moreira and López-García, 2015). It is a reasonable assumption that a mutualistic relationship would be the most desired outcome of the tight co-evolutionary relationship between host and virus. While the majority of viruses, including those existing in plants, do not cause disease and are speculated to have a non-harmful relationship with their host plants (Roossinck, 2005, 2015), the scientific literature is clearly dominated by the pathogenic viruses that cause diseases of economic importance (Scholthof *et al.*, 2011). There can be diverse strategies that viruses utilize for pathogenicity, the ability of the virus to cause a disease in its host. Several factors such as horizontal transmission by animal vectors and use of multiple plant species as hosts influence the fitness of the virus in the host population (Froissart *et al.*, 2010; Acosta-Leal *et al.*, 2011; Lancaster and Pfeiffer, 2012; Márquez and Roossinck, 2012). Indeed the

ecological prerequisites driving expansion and diversification of viruses are complex.

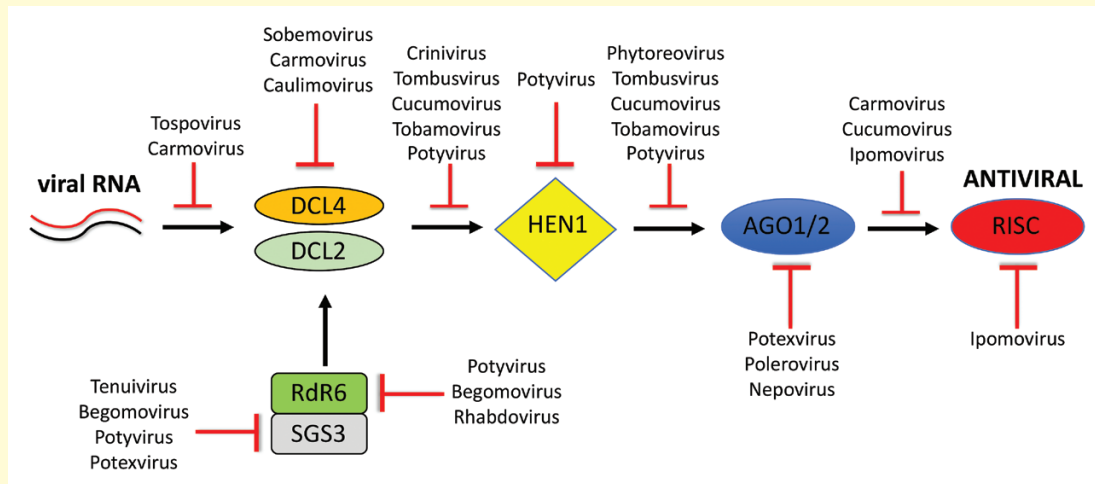
Convergent evolution of viral effector functions

Most, if not all, pathogens have acquired proteins with effector functions, which are defined by their capacity to manipulate host immune responses and resources for the benefit of infection (Mandadi and Scholthof, 2013). Plant viruses have strong potential for rapid evolution (Duffy *et al.*, 2008; Acosta-Leal *et al.*, 2011), driving diversification and the establishment of immense sequence variability. Importantly, plant viruses seem to acquire effector functions in parallel through convergent evolution rather than horizontal gene transfer, as the latter is common for bacterial and fungal pathogens (Kado, 2009; Selin *et al.*, 2016).

The outcome of this convergent effector evolution is nicely exemplified by the most famous and well-studied class of plant viral effectors, the RNA silencing suppressors, that counteract the prominent RNA silencing pathway employed in plant defense (Csorba *et al.*, 2015; Zhao *et al.*, 2016). Here we have observed that plant viruses universally evolved RNA silencing suppressors in a parallel manner. First, the suppressors lack sequence homology and, secondly, they interfere with different steps of this antiviral pathway (Box. 1). Consequently, the identification and mechanistic study of these effectors have contributed to the holistic understanding of the mechanisms and components underlying the RNA silencing pathway in plants. It is plausible that the convergent evolution of RNA silencing suppressors exemplifies a general model of virus effector evolution. Building on this hypothesis, we expect that viruses have together accumulated mechanistically diverse ways to manipulate and exploit different cellular pathways important for infection in plants (García-Ruiz, 2018). Research suggests that these targets are numerous, including autophagy (Dong and Levine, 2013), RNA granules (Poblete-Duran *et al.*,

Box 1. Diverse virus adaptation to suppress an RNA silencing pathway

The simplified scheme shows how diversely viruses have adapted to suppress the plant DCL2/DCL4-dependent RNA silencing pathway. This illustrates how plant viruses have undergone convergent evolution to suppress the function of this pathway, with the general aim of reducing the antiviral RNA-induced silencing complex (RISC), which is achieved via both common and distinct strategies/interaction points. We expect that the virome could co-evolve similarly with any plant pathway that has a central role in infection and thus consider it as a potential toolbox for studying such pathways. This simplified illustration is based on information from a review on viral RNA silencing suppressors (Csorba *et al.*, 2015).



2016), translational regulation (Zorzatto *et al.*, 2015), the ubiquitin–proteasome system (Verchot, 2016a), the unfolded protein response (Verchot, 2016b), lipid metabolism (Strating and van Kuppeveld, 2017), phytohormones (Collum and Culver, 2016), vesicular trafficking (Laliberté and Zheng, 2014; Pitzalis and Heinlein, 2017), macromolecular transport between cells (Heinlein, 2015; Kumar *et al.*, 2015), and major developmental pathways including flowering (Cecchini *et al.*, 2002). All these infection targets are also linked to plant defense responses. This lays the groundwork for using diverse virus effectors as a resource for mechanistic and functional studies of such pathways both within and outside an infection context.

Arabidopsis: a powerful model

For the vast majority of plant species, the currently known and available viruses that are capable of a compatible infection are limited. How many different viral species can we expect to infect a single host species? Humans are probably the best surveyed species, with a recent estimate of well over 200 infecting viral species (Woolhouse *et al.*, 2012). Considering the short time period for which *Arabidopsis thaliana* (Arabidopsis) has been used as a plant model in virology (Pagán *et al.*, 2010; Ouibrahim and Caranta, 2013), an impressive number of viruses have already been found to infect this plant, with at least 46 different species spanning 16 genera (Table 1). For many viral species, there are several known strains that further expand this diversity, not least because they frequently show large variations in the severity of disease (Cecchini *et al.*, 1998). This

enables broad virus diversity and comparative virology studies in the resource-rich model plant *Arabidopsis*. Owing to broad virus diversity, additional plant models such as tomato, cucumber, lettuce, potato, melon, pepper, and rice could all be considered (Hanssen *et al.*, 2010). The diverse viruses infecting a single host can be exploited to understand pertinent cellular pathways. If using well-established heterologous systems such as *Nicotiana benthamiana* for screening viral effector proteins without a prerequisite for infection of a specific host, the available virus diversity becomes practically unlimited.

Diverse viruses to dissect selected pathways

The efficiency of a virus diversity approach increases with the overall number of viruses targeting a specific pathway. How globally a selected pathway is integrated into virus infections usually becomes clear in retrospect when enough examples have emerged. However, animal viruses have been studied much more extensively than plant viruses and may therefore provide clear hints as to which cellular pathways could be approached through virus diversity in plants. An example of such a pathway is autophagy, which has so far been shown to function in >50 different animal virus infections, with roles ranging from different antiviral immune responses to direct support for infection (Dong and Levine, 2013). Importantly, animal viruses commonly manipulate different regulatory nodes of the autophagy pathway, transforming them into a potential resource for functional dissection of the pathway.

Table 1. List showing viruses that infect *Arabidopsis thaliana Col-0*

Genus	Species	Reference
Alfavirus	Alfalfa mosaic virus	Balasubramaniam <i>et al.</i> (2006)
Begomovirus	Cabbage leaf curl virus	Hill <i>et al.</i> (1998)
	Cleome leaf crumple virus	Paprotka <i>et al.</i> (2010)
	Euphorbia mosaic virus	Paprotka <i>et al.</i> (2010)
	Sri Lankan cassava mosaic virus	Mittal <i>et al.</i> (2008)
	Tomato yellow leaf curl virus	Sade <i>et al.</i> (2014)
	South African cassava mosaic virus	Pierce and Rey (2013)
Bromovirus	Brome mosaic virus	Dzianott and Bujarski (2004)
	Cassia yellow blotch virus	Iwahashi <i>et al.</i> (2005)
	Cowpea chlorotic mottle virus	Fujisaki <i>et al.</i> (2003)
	Spring beauty latent virus	Iwahashi <i>et al.</i> (2005)
Carmovirus	Cardamine chlorotic fleck virus	Skotnicki <i>et al.</i> (1993)
	Turnip crinkle virus	Li and Simon (1990)
Caulimovirus	Cauliflower mosaic virus	Melcher (1989)
Cheravirus	Apple latent spherical virus	Igarashi <i>et al.</i> (2009)
Cilevirus	Citrus leprosis virus C	Arena <i>et al.</i> (2013)
	<i>Solanum violaeifolium</i> ringspot virus	Arena <i>et al.</i> (2017)
Comovirus	Turnip ringspot virus	Rajakaruna <i>et al.</i> (2007)
Cucumovirus	Cucumber mosaic virus	Takahashi <i>et al.</i> (1994)
Curtovirus	Beet curly top virus	Lee <i>et al.</i> (1994)
	Beet severe curly top virus	Lee <i>et al.</i> (1994)
	Spinach curly top virus	Baliji <i>et al.</i> (2007)
Dichorhavirus	Clerodendrum chlorotic spot virus	Arena <i>et al.</i> (2017)
	Coffee ringspot virus	Arena <i>et al.</i> (2017)
Nanovirus	Faba bean necrotic yellow virus	Vega-Arreguín <i>et al.</i> (2007)
Nepovirus	Arabis mosaic virus	Martinez-Herrera <i>et al.</i> (1994)
	Cherry leaf roll virus	Rumbou <i>et al.</i> (2009)
	Tobacco ringspot virus	Lee <i>et al.</i> (1996)
	Tomato spotted wilt virus	German <i>et al.</i> (1995)
Polerovirus	Beet mild yellowing virus	Stevens <i>et al.</i> (2005)
	Beet western yellows virus	Bortolamiol <i>et al.</i> (2007)
	Turnip yellows virus	Stevens <i>et al.</i> (2005)
Potexvirus	<i>Plantago asiatica</i> mosaic virus	Yamaji <i>et al.</i> (2012)
Potyvirus	Lettuce mosaic virus	Revers <i>et al.</i> (2003)
	Plum pox virus	Decroocq <i>et al.</i> (2006)
	Tobacco etch virus	Contreras-Paredes <i>et al.</i> (2013)
	Turnip mosaic virus	Martinez-Herrera <i>et al.</i> (1994)
	Watermelon mosaic virus	Ouibrahim <i>et al.</i> (2014)
Sobemovirus	Turnip rosette virus	Callaway <i>et al.</i> (2004)
Tobamovirus	Oilseed rape mosaic virus	Aguilar <i>et al.</i> (1996)
	Tobacco mosaic virus	Ishikawa <i>et al.</i> (1991)
	Turnip vein clearing virus	Lartey <i>et al.</i> (1997)
Tobravirus	Pepper ringspot virus	Jaubert <i>et al.</i> (2011)
	Tobacco rattle virus	Donaire <i>et al.</i> (2008)
Tospovirus	Iris yellow spot virus	Naveed and Pappu (2012)
Tymovirus	Turnip yellow mosaic virus	Martinez-Herrera <i>et al.</i> (1994)

It is only recently that discoveries of autophagy in plant virus infections have been made, including an ssDNA virus (Haxim *et al.*, 2017), a dsDNA virus (Hafren *et al.*, 2017), and three ssRNA viruses (Hafren *et al.*, 2018; Yang *et al.*, 2018). These few examples already imply global integration of autophagy in plant virus infections, identifying mechanisms involved in inhibition of autophagy by viral proteins, viral protein interaction with autophagy components, viral component degradation by autophagy, and more generally that autophagy has both antiviral and proviral functions in plant virus epidemiology. According to our point of view, we predict that

a systematic application of diverse viruses could be used to identify a plethora of autophagy-based mechanisms that are activated and manipulated by viruses, thereby broadening our understanding of the plant autophagy pathway *per se* and its diverse roles in viral pathogenesis. RNA granules is yet another infection point we consider promising to study further using virus diversity, owing to their broad incorporation into animal virus infections (Poblete-Duran *et al.*, 2016) and also the intriguing connections that slowly accumulate for plant viruses (Beckham *et al.*, 2007; Hafren *et al.*, 2015; Ma *et al.*, 2015; Ye *et al.*, 2015; Meteignier *et al.*, 2016; Krapp *et al.*, 2017).

What potential advantages and complements do this approach bring compared with others such as *Arabidopsis* forward genetics? First and as already discussed in connection with the virome interaction with the RNA silencing pathway (Box 1), convergent evolution of the different viruses will result in the identification of different regulatory nodes of complex pathways. Secondly, if we are dealing with cellular pathways and functions that show no growth phenotypes when disrupted and cell biological phenotyping is required, the screening of a virome using such phenotyping platforms is simple compared with a forward genetics screen. This could hold especially true in the absence of an automated high-throughput platform for forward genetics. Thirdly, if the deletion of a pathway component is lethal for plants, it can still be manipulated by viruses without too severe growth phenotypes. One example is provided by the RNA granule pathways that can show quantitative phenotypes during plant virus infections (Hafrén *et al.*, 2015), and seedling lethality when knocked out (Xu and Chua, 2011). Another interesting approach will be examining plant pathways that are not globally conserved, but rather between monocot and dicot plants or even solely in between clades (e.g. glucosinolates in Brassicaceae) and how these pathways are altered by viruses capable of infection.

Concluding remarks

Molecular and cell biology-based virology continues to reveal fundamental mechanisms of cellular pathways both within and outside an infection context. Evidently, in many cases, these discoveries have arisen through the mechanistic dissection of viral effector protein manipulations of the host cell. In accordance with the central hypothesis of this viewpoint that viruses acquire effector protein functions through functionally convergent evolution and presuming that convergent evolution successfully equipped diverse viruses with effectors targeting a specific pathway, as observed for RNA silencing, these effectors should provide a unique tool for its mechanistic study. Based on the discussion above, we propose that a prominent resource could be an expression library that consists of proteins from a wide and comprehensive plant virus diversity to be used for screening pathway phenotypes as a starting point to identify pathway regulators. In parallel, this could systematically evaluate the phenomenon of virus effector convergent evolution.

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