

# **Towards an integrated molecular model of plant-virus interactions**

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## **Abstract**

The application in recent years of network theory methods to the study of host-virus interactions is providing a new perspective to the way viruses manipulate the host to promote their own replication. An integrated molecular model of such pathosystems require three detailed maps describing *i*) the interactions between viral elements, *ii*) the interactions between host elements, and *iii*) the cross-interactions between viral and host elements. Here, we compile available information for *Potyvirus* infecting *Arabidopsis thaliana*. With an integrated model, it is possible to analyze the mode of virus action and how the perturbation of the virus targets propagates along the network. These studies suggest that viral pathogenicity results not only from the alteration of individual elements but it is a systemic property.

## **Highlights**

- Systems virology seeks to describe networks of host-virus interactions.
- Viral perturbations affect highly connected host components triggering a cascade effect.
- Identification of network structures opens possibilities for new antivirals.
- Networks of host-virus interactions evolve as viruses adapt to the host.

## **Introduction**

The construction of a molecular model that captures all physical interactions established between the components of the host cell and the virus is the cornerstone of the emerging discipline of systems virology [1•,2]. With such a model, it could be possible to understand how the virus manipulates the host resources in its own benefit, and to reveal what are the actions it performs for bypassing host defenses [3,4••,5,6]. Apart, the own proteins and small RNAs of a virus interact among themselves to complete the replication cycle [7], and these interactions may determine the host-virus interplay and may establish new paths to communicate separated cellular functions, leading to the emergence of novel properties of the system [8•]. Together, we need regulatory, interaction and metabolic models of the host cell to study how viral perturbations propagate and finally produce the genetic and metabolic profiles typically associated to disease symptoms [9•,10]. This provides a computational framework for the comparative study of diverse viral strategies, and even for making predictions of infection outcomes after mutations in the viral genome. Accordingly, future antiviral therapies will be developed to block the interaction of a viral protein with an essential cellular target or, alternatively, by interfering at a given point of the host cell network to counteract the virus effect.

In this review, we will illustrate this systemic approach to the molecular host-virus interplay by analyzing the interactions between the *Potyvirus*, the largest family of plant RNA viruses, and the host plants. We will integrate available information for physical interactions of the viral proteins among them and also with plant proteins, gathered from multiple disperse sources, into a protein-protein interaction model of *Arabidopsis thaliana*. With such, we will draft out possible mechanisms by which viruses and plants interact. Finally, we will place these analyses into an evolutionary context.

## **Protein-protein interactions between plants and potyviruses**

After the self-processing by viral proteases of a translated polyprotein, potyviruses deploy 11 mature proteins: P1, a serine protease; HC-Pro, a protease with RNA silencing suppressor activity also involved in aphid-mediated transmission; P3, involved in cell-to-cell movement; P3N-PIPO, embedded into the P3 coding sequence and also involved in cell-to-cell movement; CI, an RNA helicase with ATPase activity; NIa-Pro, a protease; VPg, linked to the 5' end of the genome; NIb, the RNA-dependent RNA polymerase; CP, the capsid protein;

and two small peptides, 6K1 and 6K2, of unknown functions [11]. Interactions among these viral proteins have been reported for several potyviruses [7,12]. In total, 30 out of 66 possible interactions (including self-interactions) were detected *in planta*. Similarly, although not compiled in a systematic manner, many examples of interactions between potyviral proteins and different plant proteins have been reported. P1 interacts with the Rieske Fe/S protein (*At4g03280*) [13]. HC-Pro interacts with two important host factors related to RNA silencing, rgs-CaM (*At3g01830*) [14] and RAV2 (*At1g68840*) [15•]. In different hosts, it also interacts with the proteins CRT (*At1g09210*, *At1g56340* and *At1g08450*) [16], HIP1 (*At4g22670*), HIP2 (*At3g17880*) [17], and MinD (*At5g24020*) [18]. Additionally, the 20S proteasome subunits  $\alpha 5$  (*At1g53850*) [19], PAA (*At2g05840*), PBB (*At5g40580*) and PBE (*At1g13060*) [20] are targeted by HC-Pro. Moreover, P3N-PIPO interacts with PCaP1 (*At4g20260*) [21], and P3 does with RubisCO subunits RbcL (*AtCg00490*) and RbcS (*At1g67090*, *At5g38410*, *At5g38420*, and *At5g38430*) [22]. CI interacts with the proteins P58IPK (*At5g03160*) [23] and PsaK (*At1g30380*) [24]. In addition, both VPg and NIb interact with the poly(A)-binding proteins PABP2 (*At4g34110*), PABP4 (*At2g23350*) and PABP8 (*At1g49760*) [25]. NIb also does with HSP70 (*At3g09440*) [26]. For the cap-independent translation, VPg binds to the host factors eIF4E (*At4g18040*), eIF(iso)4E (*At5g35620*), eIF4G (*At3g60240*), eIF(iso)4G1 (*At5g57870*), and eIF(iso)4G2 (*At2g24050*) [27,28], being HC-Pro a partner of the 4E factors as well [29]. VPg also binds to the finger proteins OBE1 (*At3g07780*) and OBE2 (*At5g48160*) [30], and the helicase RH8 (*At4g00660*) [31]. Finally, CP interacts with DnaJ proteins (*At3g44110*, *At4g13830*, *At4g36040*, and *At5g22060*) [32].

We can now couple all these interactions with a recently reported protein-protein interaction network of *A. thaliana* (*At-PPIN*), which involves about 11,300 experimentally predicted contacts among 4,900 proteins [33••]. In Fig. 1, we show the resulting network involving the potyviral and host proteins at play. HC-Pro, P3 and VPg appear as the major players for interacting with the host, while the other viral proteins have a moderated relationship and roughly remain to cross-interact at the virus level. P3 and VPg interact with two highly connected proteins (RbcS and OBE1) according to that interactome, but HC-Pro does with many proteins with low degree, sharing targets with VPg. Some of those targeted proteins interact with RNAs (e.g., eIF4E and eIF(iso)4E) or act as transcription factors (e.g., RAV2). Hence, subsequent layers that can be added to complete the model are transcription and

miRNA regulations, and miRNA-protein interactions. The interactions with pivotal factors such as eIF, 20S proteasome and RubisCO also suggest that the virus may carry out a major disturbance in the cellular balance, which otherwise may trigger the immune system response [4••,5]. Still, this protein network needs to be completed with more *A. thaliana*-potyvirus interactions in order to reach a comprehensive model that could lead us to understand the mode of action of plant viruses, and how it would be compared with those characteristic for other pathogens.

### **Network perturbations upon viral infection**

The correct functioning of the cell requires the orchestration of thousands of genes to process the information it receives from its environment and to undertake the appropriate biological tasks. To this end, cells have evolved gene networks that allow circulating the information flow to finally trigger the functions of interest, in addition to establish internal control mechanisms. These genome-scale networks tend to be hierarchical, that is, presenting asymptotic scale-free and clustering patterns [35•]. Therefore, where are localized the plant-virus interactions within these networks and what are the processes viruses manipulate are questions that naturally arise. This could point out, one the one hand, general modes of virus action, or, on the other hand, specific strategies that certain virus relies on. Extensive work with animal viruses has revealed that virus targets tend to be highly connected and central proteins [36,37,38••]. In plants, bacterial pathogens also interact with hub proteins [39•], and it is expected to confirm this pattern for several plant viruses with a comprehensive model of interactions. Already from Fig. 1 we can figure out some properties, such as potyviruses also target elements in the core of the cellular network. Being 4.6 the average degree of a given protein in *At*-PPIN, RbcS and OBE1 can be considered hubs of this network as they have 23 and 27 interactors, respectively. Moreover, according to an inferred regulatory network of *A. thaliana* [40], RAV2 is a master transcription factor (at 20% with more potential regulations).

By targeting at high levels of the hierarchical organization, although not necessarily at the same point, viruses can provoke multiple disruptions in the normal functioning of the cell; certainly because those cellular networks are on average robust to random perturbations, but extremely fragile to attacks in the central hubs [35•]. It is then indebted, also because plants have interlinked signaling pathways [41], that common processes will be perturbed upon

different viral infections, as illustrated by the induction of common transcriptomic profiles, involving biotic and abiotic stress response genes, with several RNA viruses [42•,43]. From those upper points, the virus is able to hijack a variety of central pathways (e.g., hormone signaling, cell cycle control, or protein modification and transport) for its own profit [4••], while the control mechanisms of the host cell can detect any interruption of them, and then adopt the corrective measures to restore the operative point. To analyze how the information flow of infection propagates (from virus targets to defense and disease-associated genes), omics data can also be contextualized onto global networks such as *At*-PPIN [43,44].

However, even targeting hub proteins, a virus may employ a distinctive strategy to maximize its fitness. General or specific attacks can be assorted according to the functional category of the targeted proteins. In a recent experimental work with human pathogens, it has been shown this diversification depending on the nature (genome architecture) of the virus, where RNA viruses preferentially target signaling pathways and hence prevent cell coordination, while DNA viruses, on the contrary, tend to interplay directly with disease-associated genes [45•]. Potyviruses perform a broad attack by perturbing the whole proteome of their host plants, with direct interactions at the levels of protein translation, degradation and folding. Despite, it remains questionable whether plant viruses follow that classification. Finally, the natural host of a virus imposes additional constraints through host-virus co-evolution [46], which is supported by significant differences observed in the set of altered cell functions when analyzing viruses that naturally infect *A. thaliana* and those that do not [43].

### **Virus adaptation to a new host plant affects interactions**

As pointed out by T. Dobzhansky in his famous 1973 assay, “nothing in biology makes sense except in the light of evolution”. Viruses high mutation rates, short replication times and large population sizes, which bestow them with a remarkable evolutionary potential [47], make this assertion particularly relevant when dealing with host-virus interactions. Considering that the reported interactions, as well as the strength of them, are the result of a particular interplay between a virus and a host cell, we need to look at the network shown in Fig. 1, in fact, as a plastic map, where the edges can be weighted to account for different potyviruses. Strong interactions for a given potyvirus can be, at the same time, weaker or even non-existent for others. For instance, taking the common host *A. thaliana*, VPg of Turnip mosaic virus (TuMV) preferentially binds to eIF(iso)4E, while VPg of Tobacco etch

virus (TEV) does to eIF4E [27]. And this discrepancy in the preferential target should be a consequence of the fact that *A. thaliana* is a natural host of TuMV, but not of TEV. Then, to cope with the diversity in the genetic background from host to host, viruses can evolve to rearrange their interactions for a better adaptation [48].

This relevance is clearly illustrated by the adaptation of TEV, following experimental evolution, to *A. thaliana* (as stated, a non-natural host). After 17 serial undiluted passages, TEV adapted to the susceptible ecotype *Ler-0* [49•]. While the ancestral TEV was able to systemically infect the plants with asymptomatic progression, the lab-evolved strain (TEV-*At17*) improved its accumulation by a factor of three, and induced severe symptoms, including stunting, etching and leaf malformation. Six point mutations were fixed in the virus genome after the passages: three synonymous in P1 (one) and NIa-Pro (two), and three nonsynonymous in VPg, P3 and 6K1. The triple nonsynonymous mutant reproduced TEV-*At17* phenotype. Looking at the plant transcriptome, TEV provoked the differential expression of 678 genes (356 up and 322 down). However, TEV-*At17* caused the over-expression of 950 genes and the under-expression of 1,441 [43]. It is expectable that, by adapting to this non-natural host, TEV-*At17* changes and improves its interactions with the host components. In this case, a more efficient interaction with the poly(A)-binding proteins and the translation initiation factors could explain, at least in part, the observed symptoms.

## Conclusions

With the yet scarce available data describing the interactions between *A. thaliana* and potyvirus proteins, we have been able to delineate a preliminary draft for the network of interactions that potentially can be established in this pathosystem. We have depicted some structural features that seem general for any pathosystem, such as viruses tend to target highly connected proteins. The preliminary network here presented could, nevertheless, help in disentangling some of the properties associated to the infection of *A. thaliana* by potyviruses. It is expectable that, in the coming years, fast and easy screening techniques allow to considerably enlarge the list of interactors [50], thus putting forward a more precise description of the integrated molecular model. Finally, a systems biology approach will be of significant value to shed light on the intricate mechanisms operating during plant-virus co-evolution [46], and it will help to identify the commonalities and specificities of the

interactions that emerge after the diversification of viruses upon colonization and adaptation to new hosts [43].

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## References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
  - of outstanding interest
1. • Tan SL, Ganji G, Paepfer B, Proll S, Katze MG: **Systems biology and the host response to viral infection**. *Nat Biotechnol* 2007, **25**:1383–1389.

In this instructive commentary, the authors address the viral infection through a systems biology perspective. They show how to take advantage of omic techniques and computational methods to dissect the host–virus interaction and to design antiviral drugs.

2. Bailer SM, Haas J: **Connecting viral with cellular interactomes**. *Curr Opin Microbiol* 2009, **12**:453–459.
3. Whitham SA, Wang Y: **Roles for host factors in plant viral pathogenicity**. *Curr Opin Plant Biol* 2004, **7**:365–371.
4. •• Culver JN, Padmanabhan MS: **Virus-induced disease: Altering host physiology one interaction at a time**. *Annu Rev Phytopathol* 2007, **45**:221–243.

A great review of known plant-virus interactions, linking these interactions with plant physiology. It is reported how different plant viruses interplay with central processes of the host cell.

5. Dodds PN, Rathjen JP: **Plant immunity: towards an integrated view of plant-pathogen interactions**. *Nat Rev Genet* 2010, **11**:539–548.
6. Elena SF, Carrera J, and Rodrigo G: **A systems biology approach to the evolution of plant-virus interactions**. *Curr Opin Plant Biol* 2011, **14**:372–377.
7. Guo D, Rajamäki ML, Saarma M, Valkonen JPT: **Towards a protein interaction map of potyviruses: protein interaction matrixes of two potyviruses based on the yeast two-hybrid system**. *J Gen Virol* 2001, **82**:935–939.
8. • Uetz P, Dong YA, Zeretzke C, Atzler C, Baiker A, Berger B, Rajagopala SV, Roupelieva M, Rose D, Fossum E, Haas J: **Herpesviral protein networks and their interaction with the human proteome**. *Science* 2006, **311**: 239–242.

This article identifies the intraviral protein interactions for two herpesviruses using yeast two-hybrid assays and contextualizes them in the host interactome. The results show that, whereas the viral proteins form a clustered network, the network between the viral proteins and their host targets displays scale-free properties.

9. • Gulbahce N, Yan H, Dricot A, Padi M, Byrdsong D, Franchi R, Lee D-S, Rozenblatt-Rosen O, Mar JC, Calderwood MA, *et al.*: **Viral perturbations of host networks reflect disease etiology.** *PLoS Comput Biol* 2012, **8**:e1002531.

This article shows, for viral human diseases, that virus targets tend to be close (closer than expected by chance) to the genes causing the disease, using a global model involving transcription regulations, protein-protein interactions and metabolic pathways.

10. Navratil V, de Chasse B, Combe CR, Lotteau V: **When the human viral infectome and disease networks collide: towards a systems biology platform for the aetiology of human diseases.** *BMC Syst Biol* 2011, **5**:13.
11. Urcuqui-Inchima S, Haenni AL, Bernardi F: **Potyvirus proteins: a wealth of functions.** *Virus Res* 2001, **74**:157–175.
12. Zilian E, Maiss E: **Detection of Plum pox potyviral protein-protein interactions in planta using an optimized mRFP-based bimolecular fluorescence complementation system.** *J Gen Virol* 2011, **92**: 2711–2723.
13. Shi Y, Chen J, Hong X, Chen J, Adams MJ: **A potyvirus P1 protein interacts with the Rieske Fe/S protein of its host.** *Mol Plant Pathol* 2007, **8**:785–790.
14. Anandalakshmi R, Marathe R, Ge X, Herr JM Jr, Mau C, *et al.*: **A calmodulin-related protein that suppresses posttranscriptional gene silencing in plants.** *Science* 2000, **290**:142–144.
15. • Endres MW, Gregory BD, Gao Z, Foreman AW, Mlotshwa S, *et al.*: **Two plant viral suppressors of silencing require the ethylene-inducible host transcription factor RAV2 to block RNA silencing.** *PLoS Pathog* 2010, **6**:e1000729.
- This article reports the interaction between HC-Pro and RAV2 to suppress RNA silencing, suggesting this is not caused by inhibition of silencing-related genes, but by activation of defense responses that interfere with antiviral silencing.
16. Shen W, Yan P, Gao L, Pan X, Wu J, *et al.*: **Helper component-proteinase (HC-Pro) protein of Papaya ringspot virus interacts with papaya calreticulin.** *Mol Plant Pathol* 2010, **11**:335–346.
17. Guo D, Spetz C, Saarma M, Valkonen JP: **Two potato proteins, including a novel RING finger protein (HIP1), interact with the potyviral multifunctional protein HC-Pro.** *Mol Plant-Microbe Interact* 2003, **16**:405–410.
18. Jin Y, Ma D, Dong J, Li D, Deng C, *et al.*: **The HC-pro protein of Potato virus Y interacts with NtMinD of tobacco.** *Mol Plant-Microbe Interact* 2007, **20**:1505–1511.

19. Dielen AS, Sasaki FT, Walter J, Michon T, Menard G, et al.: **The 20S proteasome alpha5 subunit of *Arabidopsis thaliana* carries an RNase activity and interacts in planta with the Lettuce mosaic potyvirus Hc-Pro protein.** *Mol Plant Pathol* 2011, **12**:137–150.
20. Jin Y, Ma D, Dong J, Jin J, Li D, Deng C, Wang T: **HC-Pro protein of Potato virus Y can interact with three *Arabidopsis* 20S proteasome subunits in planta.** *J Virol* 2007, **81**:12881–12888.
21. Vijayapalani P, Maeshima M, Nagasaki-Takekuchi N, Miller WA: **Interaction of the trans-frame potyvirus protein P3N-PIPO with host protein PCaP1 facilitates potyvirus movement.** *PLoS Pathog* 2012, **8**:e1002639.
22. Lin L, Luo Z, Yan F, Lu Y, Zheng H, Chen J: **Interaction between potyvirus P3 and ribulose-1,5-bisphosphate carboxylase/oxygenase (RubisCO) of host plants.** *Virus Genes* 2011, **43**:90–92.
23. Bilgin DD, Liu Y, Schiff M, Dinesh-Kumar SP: **P58IPK, a plant ortholog of double-stranded RNA-dependent protein kinase PKR inhibitor, functions in viral pathogenesis.** *Dev Cell* 2003, **4**:651–661.
24. Jiménez I, López L, Alamillo JM, Valli A, García JA: **Identification of a Plum pox virus CI-interacting protein from chloroplast that has a negative effect in virus infection.** *Mol Plant-Microbe Interact* 2006, **19**:350–358.
25. Dufresne PJ, Ubalijoro E, Fortin MG, Laliberté J-F: ***Arabidopsis thaliana* class II poly(A)-binding proteins are required for efficient multiplication of Turnip mosaic virus.** *J Gen Virol* 2008, **89**:2339–2348.
26. Dufresne PJ, Thivierge K, Cotton S, Beauchemin C, Ide C, Ubalijoro E, Laliberté J-F, Fortin MG: **Heat shock 70 protein interaction with Turnip mosaic virus RNA-dependent RNA polymerase within virus-induced membrane vesicles.** *Virology* 2008, **374**:217–227.
27. Lellis AD, Kasschau KD, Whitham SA, Carrington JC: **Loss-of-susceptibility mutants of *Arabidopsis thaliana* reveal an essential role for eIF(iso)4E during potyvirus infection.** *Curr Biol* 2002, **12**:1046–1051.
28. Ray S, Yumak H, Domashevskiy A, Khan MA, Gallie DR, Goss DJ: **Tobacco etch virus mRNA preferentially binds wheat germ eukaryotic initiation factor (eIF) 4G rather than eIFiso4G.** *J Biol Chem* 2006, **281**:35826–35834.
29. Ala-Poikela M, Goytia E, Haikonen T, Rajamäki M-L, Valkonen JPT: **Helper component proteinase of the genus potyvirus is an interaction partner of translation**

**initiation factors eIF(iso)4E and eIF4E and contains a 4E binding motif.** *J Virol* 2011, **85**:6784–6794.

30. Dunoyer P, Thomas C, Harrison S, Revers F, Maule A: **A cysteine-rich plant protein potentiates potyvirus movement through an interaction with the virus genome-linked protein VPg.** *J Virol* 2004, **78**:2301–2309.
31. Huang T-S, Wei T, Laliberté J-F, Wang A: **A host RNA helicase-like protein, AtRH8, interacts with the potyviral genome-linked protein, VPg, associates with the virus accumulation complex, and is essential for infection.** *Plant Physiol* 2010, **152**:255–266.
32. Hofius D, Maier AT, Dietrich C, Jungkunz I, Bornke F, *et al.*: **Capsid protein-mediated recruitment of host DnaJ-like proteins is required for Potato virus Y infection in tobacco plants.** *J Virol* 2007, **81**:11870–11880.
33. •• Arabidopsis Interactome Mapping Consortium: **Evidence for network evolution in an Arabidopsis interactome map.** *Science* 2011, **333**:601–607.

This article describes a proteome-wide binary protein-protein interaction map for *A. thaliana*, and it is exploited to show that gene duplications can explain the network topology, suggesting an evolutionary pattern.

34. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B, Ideker T: **Cytoscape: a software environment for integrated models of biomolecular interaction networks.** *Genome Res* 2003, **13**:2498–2504.
35. • Barábasi AL, Oltvai ZN: **Network biology: understanding the cell's functional organization.** *Nat Rev Genet* 2004, **5**:101–113.

In this review, the authors describe the principal network properties and the particular features that biological networks display, including hierarchy, modularity and robustness.

36. Calderwood MA, Venkatesan K, Xing L, Chase MR, Vazquez A, Holthaus AM, Ewence AE, Li N, Hirozane-Kishikawa T, Hill DE, *et al.*: **Epstein-Barr virus and virus human protein interaction maps.** *Proc Natl Acad Sci USA* 2007, **104**:7606–7611.
37. Dyer MD, Murali TM, Sobral BW: **The landscape of human proteins interacting with viruses and other pathogens.** *PLoS Pathog* 2008, **4**:e32.
38. •• De Chasseay B, Navratil V, Tafforeau L, Hiet MS, Aublin-Gex A, Agaugué S, Meiffren G, Pradezynski F, Faria BF, Chantier T, *et al.*: **Hepatitis C virus infection protein network.** *Mol Syst Biol* 2008, **4**:230.

This article identifies viral targets by yeast two-hybrid assays and shows that targeted proteins are highly connected and central in the human interactome. In addition, a functional analysis in terms of metabolic pathways is performed.

39. • Mukhtar MS, Carvunis A-R, Dreze M, Epple P, Steinbrenner J, Moore J, Tasan M, Galli M, Hao T, Nishimura MT, *et al.*: **Independently evolved virulence effectors converge onto hubs in a plant immune system network.** *Science* 2011, **333**:596–601.

This article identifies common bacterial effector targets in *A. thaliana* by yeast two-hybrid assays and shows that targeted proteins are hubs in the plant interactome.

40. Carrera J, Rodrigo G, Jaramillo A, Elena SF: **Reverse-engineering the *Arabidopsis thaliana* transcriptional network under changing environmental conditions.** *Genome Biol* 2009, **10**:R96.

41. Jaillais Y, Chory J: **Unraveling the paradoxes of plant hormone signaling integration.** *Nat Struct Mol Biol* 2010, **17**:642–645.

42. • Whitham SA, Quan S, Chang HS, Cooper B, Estes B, Zhu T, Wang X, Hou YM: **Diverse RNA viruses elicit the expression of common sets of genes in susceptible *Arabidopsis thaliana* plants.** *Plant J* 2003, **33**:271–283.

This article analyzes a compendium of gene expression profiles in plants for the first time to compare the infection mechanisms of different viruses in a common host, and highlights some generalities.

43. Rodrigo G, Carrera J, Ruiz-Ferrer V, del Toro FJ, Llave C, Voinnet O, Elena SF: **A meta-analysis reveals the commonalities and differences in *Arabidopsis thaliana* response to different viral pathogens.** *PLoS ONE* 2012, **7**:e40526.

44. Warsow G, Greber B, Falk SS, Harder C, Siatkowski M, Schordan S, Som A, Endlich N, Scholer H, Repsilber D, *et al.*: **ExprEssence – revealing the essence of differential experimental data in the context of an interaction/regulation network.** *BMC Syst Biol* 2010, **4**:164.

45. • Pichlmair A, Kandasamy K, Alvisi G, Mulhern O, Sacco R, Habjan M, Binder M, Stefanovic A, Eberle C-A, Goncalves A, *et al.*: **Viral immune modulators perturb the human molecular network by common and unique strategies.** *Nature* 2012, **487**:486–490.

This article presents a high-throughput study to identify the human gene targets for several RNA and DNA viruses, highlighting general and specific molecular mechanisms.

46. Pagán I, Fraile A, Fernández-Fueyo E, Montes N, Alonso-Blanco C, García-Arenal F: ***Arabidopsis thaliana* as a model for the study of plant–virus coevolution.** *Phil Trans R Soc B* 2010, **365**:1983–1995.
47. Domingo E, Holland JJ: **RNA virus mutations and fitness for survival.** *Annu Rev Microbiol* 1997, **51**:151–178.
48. Meyer JR, Dobias DT, Weitz JS, Barrick JE, Quick RT, Lenski RE: **Repeatability and contingency in the evolution of a key innovation in phage lambda.** *Science* 2012, **335**:428–432.
49. • Agudelo-Romero P, Carbonell P, Pérez-Amador MA, Elena SF: **Virus adaptation by manipulation of host’s gene expression.** *PLoS ONE* 2008, **3**:e2397.
- This article reports results for an evolution experiment of TEV on *A. thaliana* in which the evolved virus triggers a different plant transcriptomic pattern compared to the ancestral one.
50. Nagy PD: **Yeast as a model host to explore plant virus-host interactions.** *Annu Rev Phytopathol* 2008, **46**:217–242.

**Figure 1.** Protein-protein interaction network of the *A. thaliana*-potyvirus pathosystem (based on experimental reports). Interactions between the viral proteins are shown in blue, between the viral and host proteins (virus targets) in red, and between the virus targets and their direct partners in black. We provide the Cytoscape [34] file upon request, expecting its update with future experiments and to be a practical source for exchange.