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Evolution of plant–virus interactions: host range and virus emergence

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Changes in host range are central to virus emergence. Host range, together with its evolution, is determined by virus intrinsic factors, such as genetic traits determining its fitness in different hosts. Experimental analyses have shown the relevance in host range evolution of across-host fitness trade-offs. Host range is also determined by ecological factors extrinsic to the virus such as the distribution, abundance, and interaction of species, and understanding their role in host range evolution is a current challenge. Indeed, intrinsic and extrinsic factors, and the complexity of biotic and abiotic interactions, must be considered in order to provide generalisations on patterns of transmission, host range evolution, and disease emergence. This exciting new field of research is still in its infancy.

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Introduction

Plant virus emergence is a complex process driven by the interaction of multiple ecological and genetic factors that ultimately result in the virus encountering a new host and adapting to it to ensure effective between-host transmission in the new host population [1]. Host range evolution is thus central to plant virus emergence and, as such, has received considerable research attention in the recent past.

Host range, defined as the number of host species used by a pathogen, is in theory a simple metric central to understanding pathogen epidemiology and pathogenicity. However, this simple metric should not be treated as an immutable trait because ecological factors such as the distribution, abundance and interaction of species determine the range of potential hosts a virus comes into contact with Ref. [2]. Also, a virus host range is difficult to estimate as identifying all 'non-hosts' is practically impossible. Knowledge on host ranges may be particularly limited for plant viruses, and studies have strongly favoured those that cause diseases in crops, while interactions in wild ecosystems remain relatively unexplored [3,4]. Host range evolution may result in a shift, or change between hosts, or in the acquisition of new hosts or loss of existing ones [1]. Host range, together with its evolution, is determined by factors intrinsic to the virus, such as genetic traits that determine its fitness in different hosts, or extrinsic to the virus, related to its ecology and epidemiology. Explanations of host range evolution have focussed mostly on the intrinsic, genetic factors, and only recently have studies approached the role of extrinsic factors, and of how intrinsic and extrinsic factors interact.

Virus-intrinsic factors in host range evolution

A major virus-intrinsic determinant of host range is genetic specificity, that is, only some viruses can infect and multiply in a certain host and, similarly, often only some virus genotypes can infect and multiply in each host genotype. Specificity of infection has been analysed mostly within the context of the gene-for-gene (GFG) and the matching-alleles (MA) co-evolutionary models [5]. These models, initially developed to explain host genotype × pathogen genotype interactions, have been applied extensively to analyse plant virus host range evolution at the pathosystem level [6]. If these models are applied at the interspecies level, a GFG-like system allows host range expansions, while an MA-like system determines host shifts. So, studies of the structure of the network of interactions among large sets of bacteria and bacteriophage species indicated modular (i.e. subsets of specific interactions) or nested (i.e. species ranked by their range of specificity) structures, depending on the geographical and taxonomical scales of the analysis, and it was suggested that the evolution of generalism represented by the nested structure would be due to a GFG-like interaction, while the evolution of specialism will be driven by MA-like interactions, resulting in modular infection networks [7,8]. Recently, the structure of a 37 virus × 28 plant species infection matrix was reported [9••]. The whole network was nested, but included significant modules that corresponded to viruses infecting particular plant families, indicating two major groups of viruses, generalists and specialists on different host

families. Although this analysis was based on experimental host-ranges, it is the first study seeking to understand host range evolution in plant viruses at a global scale.

Specificity of infection means that pathogen fitness varies across all potential hosts, which leads to the concept of adaptive trade-offs among hosts. Because some fitness components are host-dependent, a pathogen cannot simultaneously maximise its fitness in all its potential hosts, but it may adapt to one or a few related ones, in which its fitness will be maximal. If adaptation to one host implies a fitness cost in other hosts, an adaptive trade-off among hosts will be generated, which will hinder host range expansion and favour the evolution of specialism rather than generalism. The study of across-host fitness trade-offs and how they affect transmission across host species form an active field that has provided abundant evidence of penalties associated with the capacity to infect and multiply efficiently in a new host, expressed as reduced fitness in the original host [1,6]. Interestingly, trade-offs may also occur between the two different hosts, in which the virus must replicate to complete its life cycle, as in the plant host and insect vector of rice stripe virus [10]. Two major mechanisms causing across-host fitness trade-offs that have been extensively analysed are antagonistic pleiotropy [11] of host-range mutations and epistatic interactions among them [12]. The role in host range evolution of antagonistic pleiotropy, epistatic and higher order interactions of adaptive mutations has been reviewed recently [13].

Evidence of across-host fitness trade-offs mostly derives from experiments, in which few virus–host interactions are tested. For instance, a virus genotype adapted to a new host by serial passaging is assayed in the new and the original host. When a higher number of interactions are examined, experiments yield more complex results that may complicate predictions on host range evolution. So, the assay of twenty random point mutants of tobacco etch virus (TEV) on eight different plant species showed a host-dependent frequency distribution of deleterious, neutral and beneficial mutations, distributions being more similar for taxonomically related hosts [14••]. Most mutations were deleterious in the original and taxonomically related hosts, and a larger fraction of mutations were beneficial in hosts from unrelated families, in which the fitness of the wild type TEV genotype was low. In agreement with these results, it has been shown that adaptation to a new host may result in adaptation to closely related hosts, which will favour virus jumps to related species [15]. In another study, seven genotypes of pepper mild mottle virus (PMMoV) with coat protein mutations determining the overcoming of different resistance alleles in pepper, were assayed in five susceptible pepper genotypes [16•]. The resistance-breaking mutations had pleiotropic effects on virus multiplication, but the sense and magnitude of these effects depended on the specific mutation and the susceptible host genotype. Moreover, the distribution of effects of host range mutations may depend on demographic factors of the virus population associated with the host genotype [17•]. These studies show that host range evolution in genetically heterogeneous, susceptible, host populations, such as those a virus will encounter in nature, will be difficult to predict on the basis of adaptive trade-offs.

Predictions also become difficult when other more realistic scenarios of host range evolution are considered, as the fitness effects of host-range mutations are modulated by extrinsic, environmental factors. For instance, in nature plants are often multiply infected by different viruses [18], and virus–virus interactions in multiple infections may determine the evolution of viral traits such as within-host multiplication, virulence and host range [19•]. Costs associated with host range expansion may also be affected by co-infection. Thus, when different resistance-breaking mutants of PMMoV were assayed in co-infection, the sense and magnitude of the pleiotropic effects of resistance-breaking mutations on virus multiplication depended on the type (single or multiple) of infection, and on the combination of mutants [16•]. Thus, across-host trade-offs were modulated by an environmental factor, multiple or single infection.

Most work on across-host fitness trade-offs has focused on the effects of host adaptation mutations on within-host virus multiplication, that is, on the reproductive component of viral fitness. However, host range evolution may be conditioned also by costs on other fitness components, as the evolution of organisms may be constrained by conflicting trade-offs between different fitness components [20], for instance between reproduction and survival. The reproduction-survival trade-off could be relevant in plant viruses, as host range mutations often occur in the coat protein gene [6]. Thus, it was shown that selection for a broader host range involved altered particle stability and survival in PMMoV, that is, selection for traits not directly related to the plant–virus interaction [21]. However, the analysis of nine-coat protein host adaptation mutations on virus multiplication and particle stability showed pleiotropic effects in these traits, but there was no correlation between virus multiplication and particle stability, or of these traits and host-range breath [22•]. These results do not support a reproduction-survival trade-off, but again indicate that across-host fitness trade-offs may depend on environmental conditions.

The still-limited experimental evidence of the modulation of across-host trade-offs by the environment agrees with predictions of genetic models of host–pathogen coevolution that incorporate ecological factors such as asynchrony in host and pathogen life cycles, or spatial structure in host and pathogen populations [23,24]. These models predict that environmental heterogeneity may

lead to the maintenance of polymorphisms for host–pathogen specificity in the absence of fitness costs, underscoring the need to consider ecological factors for understanding host range evolution.

Connecting intrinsic and extrinsic factors of host range evolution

One main reason why host range evolution is poorly understood is that it is contingent on how species interact with their environment [25,26]. Virus emergence and the spread of disease occur through a number of mechanisms that are affected by the patchiness of interacting organisms [27]. Viruses are, therefore, subject to varying opportunities to alter their host range and are expected to evolve various strategies in resource use given this environmental heterogeneity [28,29]. As a consequence, environmental heterogeneity also represents a large obstacle to forming useful generalisations explaining host range evolution and its role in disease dynamics [30].

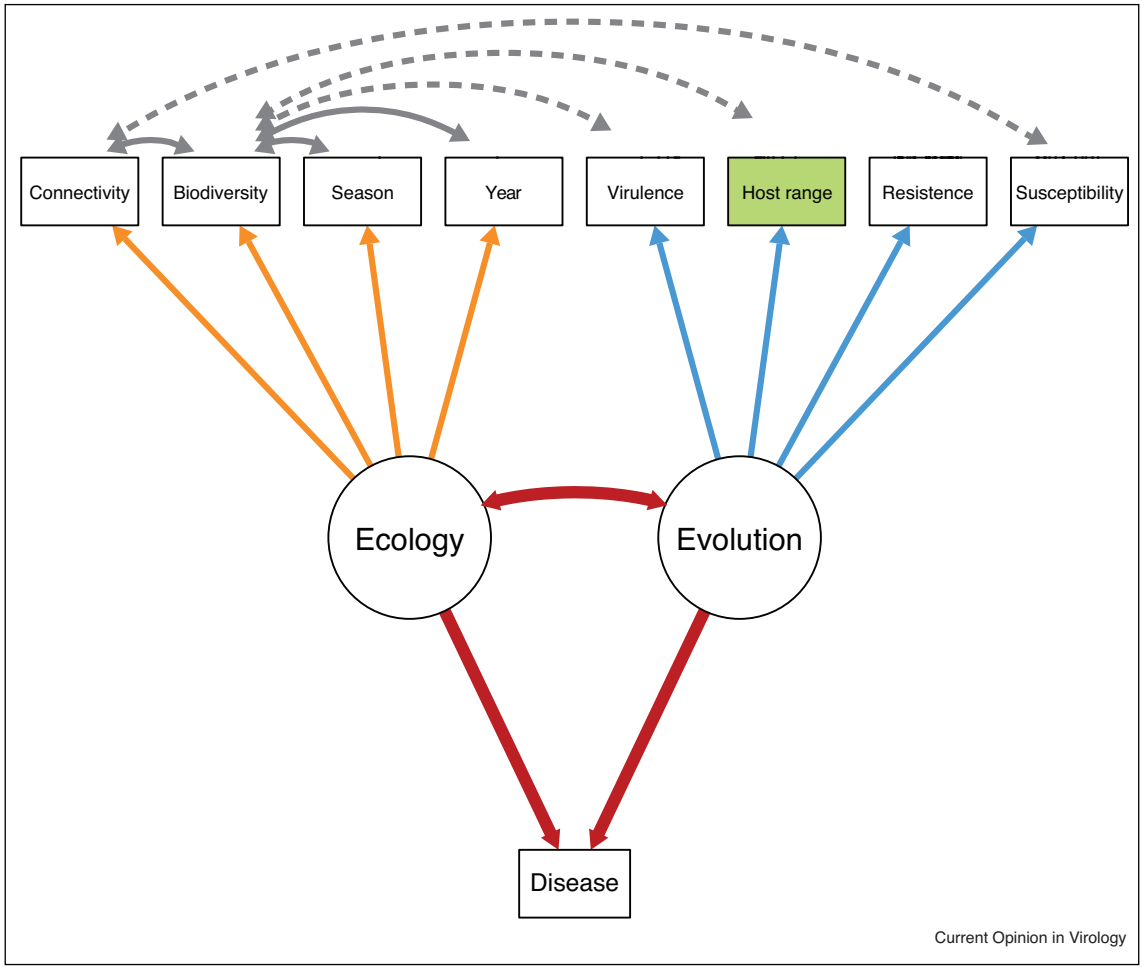
When host species co-exist in the same community, and/or are closely related, the opportunity [i.e. Ref. 31•] for viruses to interact with them is more likely than between unrelated hosts in other communities [9••], although there are known exceptions to these patterns [e.g. Ref 32]. Species coexistence in a community (indefinite persistence of a set of species) depends on selection within that community, and/or on ecologically neutral processes of community assembly in the absence of strong virus or host fitness trade-offs [33••]. Both perspectives agree that environmental heterogeneity and community connectivity have a part in the evolution of a species resource breadth. If virus fitness trade-offs are not strong among available host species [34], virus host range evolution might be driven by stochastic fluctuations in community composition [2], local extinctions and speciation, and the movement ecology of viruses (e.g. behavioural characteristics of vectors, [35]).

Causes of emerging disease outbreaks and persistent diseases [36], and of pathogen species invasions [37] all involve multi-species interactions embedded in communities. Community-level studies include a spectrum of scales from those at the landscape to interactions that occur within the same individual. Disease emergence is a landscape-scale process because transmission is associated with connectivity among communities [38]. At the smaller scale extreme, multiple infections in the same individual are important as they produce synergistic to antagonistic interactions between viruses and influence transmission [18]. The large number of plausible types of species interactions (i.e. ecology) involved in transmission add to the complexity of disease epidemiology [39] and host range evolution [26]. Community-level ecology and studies in pathology typically quantify interactions in terms of species phenotypes, or 'traits,' which can translate to 'higher' level biological organisation. The approach is insightful because species and trait interactions can be separated, where variables of interest become functions of the community and generalisable above the level of species [40].

Connecting species interactions based on interdependencies among traits is required to understand ecological and evolutionary processes [41]. Species interact through competition, predation, mutualism, herbivory and parasitism that can be quantified by 'connectivity' among (host, virus, bacteria, etc) species [42] such as in an ecological network [41]. Connectivity in turn can covary with biodiversity [43] and affect contact rates and a virus's opportunity to expand or alter its host range [44]. Ecological and evolutionary studies typically quantify traits such as host resistance and tolerance [40], susceptibility [45], pathogen virulence [46], pathogen host–species-specificity [47] or resource use strategies [48]. However, a large number of these and other interacting factors have non-linear relationships and make rationalising and forming generalisations about the cause and spread of disease mathematically challenging [49••]. Figure 1 shows relationships between some of these factors that have been hypothesised to have a role in the distribution of infection. The conceptual framework highlights indirect effects of both evolutionary (genetic) and ecological (e.g. spatiotemporal, abiotic, species interactions) factors, including virus host range, in causing the spread of disease.

It is clear that the causes of disease spread are potentially the result of many direct and indirect interactions, of which only several at any one time are the focus of an experimental study in host range evolution and disease risk. Indirect interactions between viruses and other species arise because any number of ecological or evolutionary phenomena influence transmission via complex pathways. For example, the presence of the endosymbiotic bacteria *Hamiltonella* in the whitefly *Bemisia tabaci* that vectors tomato yellow leaf curl virus, affected its transmission frequency regardless of the density of whiteflies [50•]. The, transmission patterns of West Nile virus varied as a result of differences in the mosquito vector feeding patterns among communities [51]. Similarly, the manipulation of reservoir competence between communities of vertebrate hosts resulted in changes to densities of tick vectors of Lyme disease, its transmission, and host switching patterns by vectors [44]. Such indirect, localised effects feed into how host range evolution ensues via community-specific mechanisms. For example, the analysis of the prevalence of 11 generalist viruses over 47 host species in four different plant communities showed community-related 'specialised' resource use by the viruses. This suggests that exploitation strategies often involve 'trade-offs' with limited available resources such as a subset of host species within the virus's range that it is still able to infect [52•].

Figure 1



A conceptual framework that connects ecological and evolutionary factors that have been used to explain disease risk. Host range is highlighted in green. Ecological (yellow arrows) and Evolutionary effects (blue arrows) are typically quantified using observable variables (boxes) that are a product of each paradigm. General arguments (red arrows) for the spread of disease are usually framed as a consequence of either or both these paradigms. Any number of interactions among observable variables can be drawn (e.g. grey arrows). Some of these occur between 'ecological' and 'evolutionary' phenomena (dashed arrows). Unidirectional arrows indicate causality and bidirectional arrows indicate (hypothesised) correlation.

In all the cases above, virus interactions with viruses, hosts, or other organisms were contingent on connectivity, which was a function of biodiversity and spatiotemporal variability. For example, spatial and temporal heterogeneity of multiple-infections by communities of luteoviruses and poleroviruses was explained by the community composition of vector species [53]. In another study of multiple-infection diversity, coexistence of four different B/CYDV species was largely determined by their traits and resources associated with a given locality [54]. The indirect effects of biodiversity may, therefore, either increase or decrease the risk of infection depending on spatial or temporal factors [55]. For example, prevalence–diversity relationships were affected by both host diversity of a given habitat, and habitat-related host ranges of 11 plant viruses [52•]. The changes to the realised host ranges across habitats were consistent with definitions of facultative generalism [56]. As the distributions and abundances of species are shaped by multiple sources of variation, the diversity of traits (e.g. susceptibility, resistance, and tolerance traits) or resources available to the viruses are also recast in time and space.

Reciprocal and non-reciprocal effects among a large number of variables (Figure 1) tell us that host range evolution is an opaque function of both the ecology of the system (e.g. the hosts' viruses are able to infect and colonise at a space in time) and genetics of interacting species (e.g. of viruses that mediate their propensity to multiply infect with other virus species). Processes determining virus interactions with resources or traits that are important to host range evolution might also propagate from different spatial or temporal scales and involve any number of factors due to environmental heterogeneity. Ecological

interactions, therefore, may or may not result in changes to the expression of genes that result in disease emergence. The current body of evidence suggests that generating generalisable ecological patterns explaining host range evolution and the spread of disease is extremely challenging. In other words, generalisations will emerge from comparisons among pathogen systems, each with its own unique 'eco-evo-devo' idiosyncrasies.

Conclusions

Most research on plant virus host range evolution has focussed on factors intrinsic to the virus, that is, on the genetic determination of fitness differences across hosts that condition the evolution of generalism or specialism in resource use. However, the most recent work reviewed here demonstrates that environmental factors are modulators of virus fitness across hosts, and hence need to be integrated into genetic models of host range evolution. The interaction of extrinsic and intrinsic factors in host range evolution is a research goal amenable to experimentation, and we are confident that more efforts in this direction will be tackled in the near future.

More challenging a task is to understand the role of ecological, non-deterministic factors, on host range evolution. The complexity of plant virus interactions in natural environments results in analytical challenges such as multivariate datasets with dissimilar probability distributions, spatial or temporal scale dependencies, and taxonomic anomalies. The ability to generate large datasets, for instance by high throughput approaches, has prompted the development of methods for combining sets of variables (geographical, phenotypic, and phylogenetic) to understand the role of the environment in structuring species interactions. The application of these approaches to understand host-range evolution of pathogens, and of plant viruses in particular, is still in its infancy, but promises to provide relevant insights. Crucially, the joint consideration of intrinsic and extrinsic factors, and of the complexity of their interactions, is a must to provide generalisations on the patterns of transmission, infection risk, host range evolution, and ultimately, disease emergence.

We trust that this field of research will have an exciting future.

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