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Recombination as a motor of host switches and virus emergence: geminiviruses as case studies

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Genetic recombination facilitates the transfer of genetic information in a parasexual reproduction manner even between distantly related species. Within the *Geminiviridae* family, a group of plant-infecting viruses that severely constrain cropping systems worldwide, it is highly suspected that recombination was pivotal in the emergence as a devastating phytopathological problem. Whereas extensive evidence of recombination suggests that this mechanism might be adaptive in this family, direct demonstration remains scarce. Here we assemble lines of evidences indicating that recombination was crucial in driving host switches and further emergence of geminiviruses, making these viruses such successful plant pathogens.

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Introduction

Genetic recombination allows parental viruses to derive genetic information to their progeny in a parasexual reproduction manner. This mechanism is a key process in the evolution of many virus families and has been extensively recorded for members of the family *Geminiviridae* [1–4]. Geminiviruses are plant-infecting circular single stranded (ss) DNA viruses that severely constrain production in a variety of cropping systems throughout the world [5–7]. They comprise seven genera that differ in terms of phylogenetic relationships, genome structure, host range and insect vector [8]. Besides evolving at substitutions rates equivalent to those found for RNA viruses [9], in this virus family, extensive evidence of

recombination is available at every level of the diversity spectrum [10]. As recorded also for other virus groups [11], this mechanism was most probably essential in the macroevolution and the emergence process (see [1,12*,13] for a review of recombination for the ssDNA viruses in general).

Recombination in geminiviruses facilitates the transfer of genetic information even between distantly related species in such extent that their genomic organization is thought to have evolved to maximize its adaptive value and minimize potentially deleterious effects [1]. In fact, the risk to produce defective progeny is high for geminiviruses because of their highly compacted genome (~2.7 kb) with overlapping genes, multifunctional proteins and optimized interactions between different parts and proteins it encodes. While the preservation of co-evolved interactions is supported by wide experimental and analytical information, in some cases recombinants with novel abilities to interact with hosts or vector might arise. Thus, for example, the ability to infect a particular host depends in part on the balance between host defenses and virus counterdefense. Among host defenses, it is now apparent that gene silencing is an essential plant antiviral mechanism [14]. However, as for other plant viruses, geminiviruses encode proteins that can suppress gene silencing [15] in a host dependent manner [16*]. Genetic exchanges involving these proteins might drive host shift and emergence [16*,17].

The abilities of geminiviruses to rapidly generate polymorphisms through mutations [9] and combine new genetic forms through recombination were probably essential in responding to the numerous niche extensions events offered within the context of modern agriculture [1,5–7,18–21]. However, despite a large amount of indirect evidence and some degree of speculation, there are few well supported examples of this having occurred in nature (see [4,22,23,24*] for good examples).

Recombination patterns in geminiviruses

Whereas non-homologous recombination (during which genome regions get rearranged, duplicated, deleted) is mostly apparent above the genus level in the *Geminiviridae* family, homologous recombination is a widespread phenomenon as almost every geminivirus is the descendent of some inter-species or inter-strain recombinant [10]. Importantly, analyses of viral sequences obtained from both the environment and experimental studies revealed that recombination breakpoints are generally

not randomly distributed with conserved recombination hot spots and cold spots [10]. Studies demonstrated that these distribution patterns are strongly influenced by mechanistical factors preserving interaction networks [1,25,26,27**]. Remarkably, recombination is intimately associated with the replication process of geminiviruses. It notably involves the so-called 'recombination dependent replication' mechanism that is able to recover fragments of geminiviral DNA that may result from incomplete synthesis or from nucleolytic attack to create recombinant viruses [28,29]. Doing so, it has the potential to create large number of recombinant viruses displaying specific recombination patterns (e.g. the notorious recombination hot-spot around the origin of replication [10]) when multiple viruses co-infect the same cell [1].

While mechanistic predisposition profoundly affects the recombination patterns, these also bear severe imprints of selection. Recombination breakpoint distribution patterns are partially attributable to natural selection dis-favouring survival of recombinants in which co-evolved intra-genome interaction networks are disrupted [25,30]. Whereas the vast majority of recombinant forms, as most mutants, are likely of poorer fitness than the parents [26,31], recombinants bearing favourable combinations [27] might outcompete the parental viruses and become prevalent in the population.

It is clearly apparent from the literature that genetic material is exchanged between viruses participating into epidemics on distinct hosts. Although it does not prove that recombination allowed host shift or range extension, it clearly demonstrated exchanges of genetic material between distinct viral diversity pools.

Additionally in the *Begomovirus* genus of the *Geminiviridae* family, where bipartite genomes occur, mixed infections provide opportunities for heterologous genome component reassortment, also-called pseudo-recombination. Evidences of exchange, loose or gain of components during the evolution of begomoviruses is shown in natural infections [32–34]. Importantly, pseudorecombination involving non-essential components such as betasatellites, can modulate the expression of the disease in a host-dependent manner, and drive host shift [35–37] providing another determinant for host adaptation.

Recombination as a driving force of emergence

Besides experimental studies demonstrating alteration of ecology and fitness following recombination between geminiviruses [22,38–45], evidences accumulate for recombination as *in natura* mechanism of modification of host ranges [4,22,32,40,46–48,49**]. These notably include the invasive spread of tomato yellow leaf curl disease (TYLCD)-associated begomoviruses across the

Western Mediterranean during the past three decades [22,50] or the emergence of maize streak disease as a major agricultural threat throughout the African continent [4,51]. It should be highlighted that these diseases were absent in the centre of origin of the host plants (both from the Americas) and have emerged in the areas where these plants were later introduced. Recombination might have contributed to the likely host switches events and adaptation of locally circulating geminiviruses.

Recombination as a driving force in dicot geminiviruses: begomoviruses

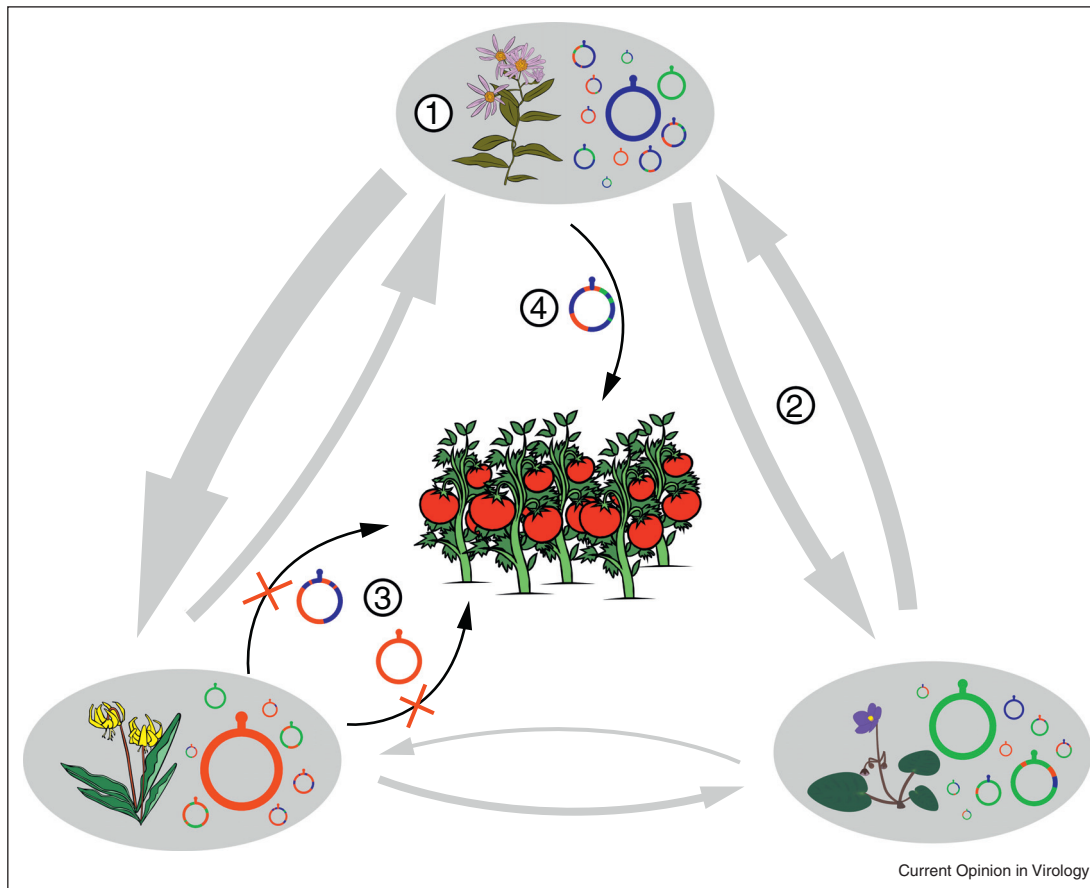
Begomovirus is one of the largest plant virus genus comprising almost 300 viral species [52]. Several lines of evidence indicate that the emergence of a highly polyphagous and invasive type of the vector of begomoviruses, the whitefly (Hemiptera: Aleyrodidae) *Bemisia tabaci*, is contributing to transferring begomoviruses among a large set of distinct hosts [7,53], increasing the opportunities of mixed infection and further diversification through recombination [21]. Some instances of such events have been recorded with, for example, the recent pandemic on cassava in Africa caused by a recombinant virus with an extremely increased severity [54,45], or the emergence of the resistance-breaking recombinant virus named cotton leaf curl Burewala virus (CLCuBuV) that causes devastating damage to cotton production in India and Pakistan [24]. One of the best studied examples is the one that refers to TYLCD-associated begomoviruses. The TYLCD has emerged during the last decades in almost every region of the world where tomato is commercially grown [50] and is caused by a complex of begomovirus species related to the highly invasive tomato yellow leaf curl virus (TYLCV) [55]. Complex recombination-derived progenies were shown to arise at high frequencies and in relatively short periods during mixed infections of TYLCD-related species [3,56] or with other distantly related begomoviruses [30,57]. Interestingly, although natural selection preserves co-evolved intra-genome interaction networks [30], numerous and diverse viable recombinants can be produced during mixed infections [30,57*] or artificially [58], highlighting the tolerance to disruption of begomoviruses genomes. Scarce information, however, is available on the fitness of recombinants arising *in natura*. Again, studies conducted on natural populations of TYLCD-associated viruses inform about this aspect. In Spain and Italy, a diversity of recombinant viruses between TYLCD-associated begomoviruses was described [22,23,59]. Importantly, both field and experimental studies demonstrated that successful recombinant viruses exhibited host shift in respect to parental viruses, being able to infect a larger set of hosts [22,23]. This was the case, for example, of the recombinant virus named tomato yellow leaf curl Málaga virus (TYLCMaV) that has an enlarged host range and outcompeted the parental viruses in *Phaseolus vulgaris* epidemics [3,22].

Recombination as a driving force in monocot geminiviruses: MSV

Maize streak virus (MSV), a well characterized leafhopper-transmitted geminivirus from the *Mastrevirus* genus of the family *Geminiviridae*, is the causal agent of maize streak disease. It ranks amongst the most serious biological threats to food security in sub-Saharan Africa [5]. Clear imprints of both ancient and recent recombination events can be detected on most MSV genomes. The ability of recombination to rapidly produce viruses with altered characteristics was confirmed in a study that us sub-optimal synthetic recombinant viruses and where fitter genome were quickly restored [27]. Another step further, it was also suggested that recombination was cardinal in the emergence of new biological

features. In fact, whereas at least eleven distinct MSV strains have been reported so far from several common grasses in Africa, only the MSV-A causes severe disease in maize [4]. Interestingly, it was suggested that this MSV-A strain is in fact a recombinant between two *Digitaria*-adapted MSV strains that replicate to low level in maize and barely cause symptoms [4]. From a phylogeographic reconstruction, it was inferred that this recombinant emerged in the 1860s in southern Africa before spreading throughout Africa in the 1950s where it is today found widespread [51,60]. While this recombination event might have produced a virus with increased severity in maize, the studies highlight the possibility that it may also have enabled MSV-A to spread more efficiently by allowing it to

Figure 1



Schematic representation of geminivirus communities in a multi-host plant system, with a virus free host (here, tomato plants in the middle of the figure) and three uncultivated plant species. Each of the uncultivated plants is the host of a set of viruses (1) with contrasting degree of fitness. Rate of virus exchanges between the hosts (2) is determined by vector populations densities and preferences and by virus adaptation to each host. The topology of the network and the available sequence space determine in part the set of viruses (several of which being recombinant) that can appear. Whereas some viruses won't be able to infect the yet disease free plant (3), some others (4) with the appropriate combinations of genetic determinants will eventually be successful and potentially emerge as a proper circulating viruses on this new host. Although the figure represents the first steps of an emergence event on a crop, a process facilitated by its high density, it must be noticed that viral emergence function as a natural process within the ecosystems on potentially every plant species, cultivated or not.

infect a wider variety of hosts. In fact, MSV-A was detected on members of eight different grass genera, thus having the largest host range of all MSV strains [4]. Although it remains unknown whether this recombination event was pivotal in the emergence of MSV-A in maize, its enlarged host range might explain the ecological success of this recombinant virus.

Conclusions – future work

The expansion of monocultures and/or spread of polyphageous vectors (such as specific types of *B. tabaci* for begomoviruses), that favour movement of indigenous viruses between plants, are major ecological drivers of recent geminivirus host switches. While the contribution of recombination is clearly apparent (Figure 1), one of the greatest challenges is understanding the interplay between recombination and viral ecology. Whereas the vast majority of geminivirus sequences obtained in the last years are from viruses infecting cultivated plants, they most likely emerge from non-cultivated plants (stands for plant pathogens in general [61]). In this context, it would be extremely informative to first isolate large sets of virus sequences at the ecosystem scale before exhaustively inferring their host ranges. Several ongoing projects using metagenomics approaches will certainly pave the way to such understanding [62,63,64]. The analyses of the recombination patterns within these viral communities could inform about virus ecology. Since recombining viruses obviously have somewhat overlapping geographical distributions, host ranges and tissue tropisms, and patterns of sequence exchange amongst viruses sampled from nature could also be used to retrace the ecological interactions between populations (see [65,66] for a good examples on bacteria). Whereas the networks of genetic exchanges amongst viruses could inform about virus populations that are the most active recombiners, their analyses could reveal key host species, environmental or cultural conditions favouring specific patterns of viral encounter and from where host switch is most likely to originate. The topology of the circuits of genetic exchanges within and between virus communities would determine the probability of viruses to form new genetic combinations and to emerge in a specific spot of the fitness landscape [67]. Knowing their great success as emerging pathogens and their presumed high prevalence in most ecosystems [63,64,68–70], geminiviruses stand as an excellent model to further study emergence at the global ecosystem scale where it functions as a natural process during virus evolution.

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