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Giant viruses and their mobile genetic elements: the molecular symbiosis hypothesis

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Among the virus world, Giant viruses (GVs) compose one of the most successful eukaryovirus families. By contrast with other eukaryoviruses, GV genomes contain a wide array of mobile genetic elements (MGEs) that encompass diverse, mostly prokaryotic-like, transposable element families, introns, inteins, restriction–modification systems and enigmatic classes of mobile elements having little similarities with known families. Interestingly, several of these MGEs may be beneficial to the GVs, fulfilling two kinds of functions: (1) degrading host or competing virus/virophage DNA and (2) promoting viral genome integration, dissemination and excision into the host genomes.By providing fitness advantages to the virus in which they reside, these MGEs compose a kind of molecular symbiotic association in which both partners benefit from the presence of each other's. Thus, protective effects provided by some of these MGEs may have generated an arm race between competing GVs in order to encode the most diverse arsenal of anti-viral weapons, explaining the unusual abundance of MGEs in GV genomes by a kind of ratchet effect.

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Introduction

Giant viruses (GVs) that belong to the monophyletic clade Megavirales (former NCLDV: Nucleo Cytoplasmic Large DNA Virus) compose a remarkable group of eukaryoviruses: prevalent in many environments from the deep ocean to the human gut, they infect a wide spectrum of hosts ranging from tiny protists to vertebrates. They possess highly variable genomes in terms of size and content (from 100 kb to 2.5 Mb), play important ecological roles in controlling host proliferation and are even suspected to be human pathogens [1–6]. Thus, this peculiar group of virus has been successful in nature and it is important to understand the reasons of this success.

Compared to other eukaryoviruses, GV genomes display two salient features. The first one is the abundance of genes horizontally acquired from cellulars organisms. In average, 10% of the GV genes have been acquired by this process, mainly from prokaryotic sources and occasionally from their hosts [7–11]. The second special feature is the level of gene duplication. For instance, the largest genome of GVs has more than 50% of its sequence occupied by genes belonging to duplicated families [12]. Thus, there is a positive correlation between the GV genome size and the number of repeated genes [13,14,15•,16]. Experimental data indicate also that there is a dynamic process of gene duplication and gene loss in response to host adaptation [17••,18]. All together, the importance of horizontal gene transfers and lineage-specific gene duplications led to the emergence of the 'genomic accordion' hypothesis [13,17••,19,20], which proposes that GVs adapt to new niches, hosts or changing environments by series of genome contractions and expansions using a combination of gene transfers, duplications and deletions. Whereas this model needs to be supported by additional experimental and comparative genomics evidences, the alternative scenario implying a common ancestry with cells has lost some audience. This scenario indicated that GVs compose a 'fourth kingdom of life' in which GVs have evolved from a cellular organism through massive genome reductions. However, the existence of a 'fourth kingdom of life' lacks reliable phylogenetic signals supporting the kinship of GVs with cells [21], in addition to the absence of a genomic proof demonstrating a general tendency of GV genomes to decrease in size and in diversity with time [7,19,22]. At the opposite, the 'genome accordion' scenario fits perfectly well with a model of genome size evolution observed in birds and mammals under the cross effects of expansion and loss of mobile genetic elements (MGEs) [23].

MGEs form a disparate group of selfish genes that tend to act as molecular parasites into the genomes in which they reside. They are abundant in cellular genomes [24] but are rare in the virus world and even almost absent in eukaryovirus [25]. Strikingly, GVs are the exception of this rule. MGEs are diverse and abundant in GV genome and GVs have apparently cope with this load for a long period of time [9,16,19]. In this paper, I collect multiple

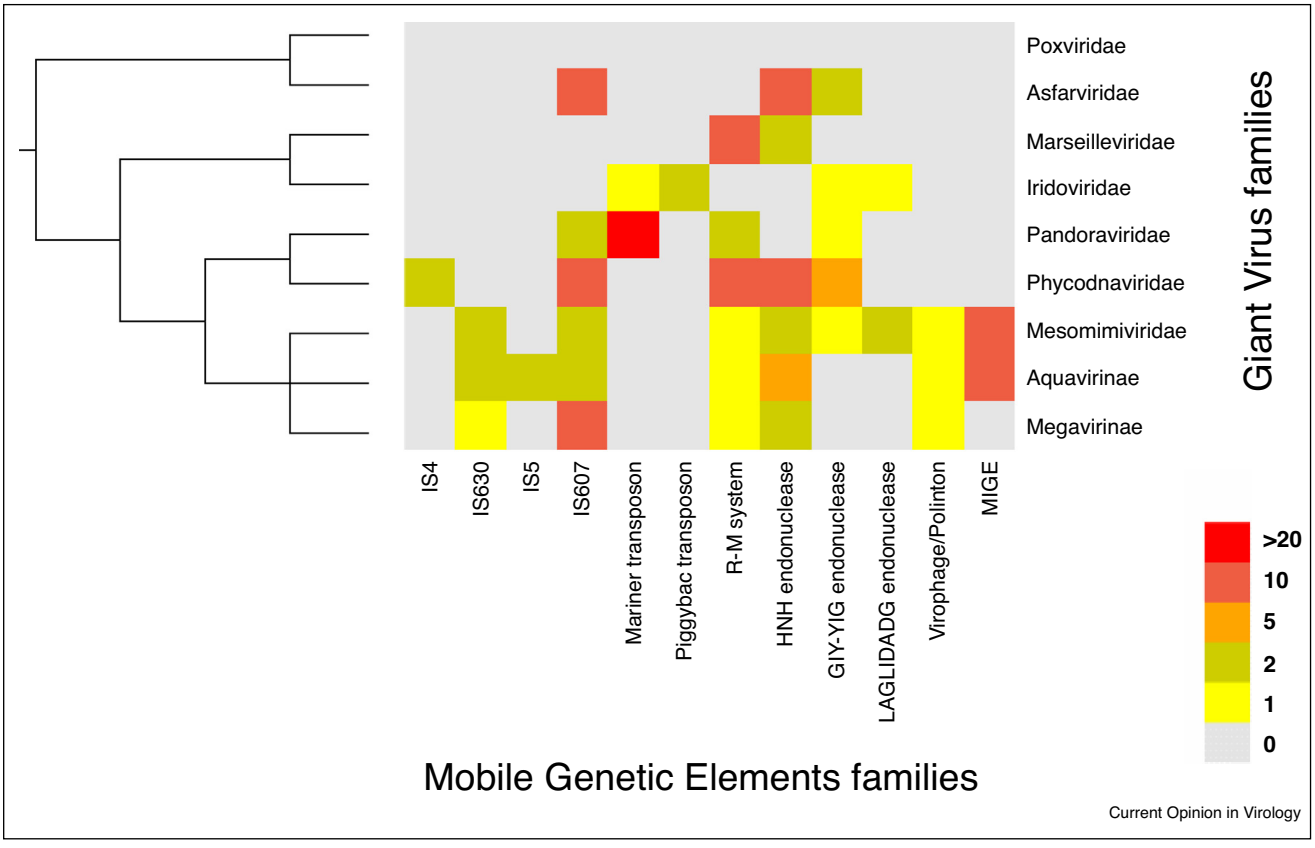
evidences that several MGEs found in eukaryoviruses have been recruited to perform viral functions. I show that the MGE/GV association has evolved towards cooperation rather than competition, allowing the MGEs to reside in a stable form in the GV genomes. This association, by providing selective advantages to the GVs also promotes the MGEs dissemination. Thus, I propose the hypothesis that the unusual abundance of MGEs in GV genomes would be explained by the existence of a kind of molecular symbiotic relationship in which both partners benefit from the presence of each other.

Distribution and origin of MGEs in eukaryoviruses

Phylogenies of hallmark genes and phyletic distributions of the genomic repertoires indicated that at least nine GV lineages exist (Figure 1) [26]. Most of these viruses harbor a large diversity of MGEs (Figure 1, Table 1). The majority are transposable elements, including diverse Insertion Sequence (IS) families and Eukaryotic-like DNA transposon families as Mariner, Piggybac or Polinton/Virophage. The last family is of special interest as it clusters a huge diversity of elements including satellite viruses of the GVs (Virophages), composite transposons (Polintons) and their highly-reduced derivatives (Transpovirons) [27••,28,29•].

In addition to transposable elements, there are also two kinds of Restriction/Modification systems (R–M systems) that are composed by a gene tandem of a restriction endonuclease and a methyltransferase. The endonuclease recognizes and cleaves at specific sites foreign DNA whereas the methyltransferase protects self DNA by transferring methyl groups at the cleavage site. These systems considered as primitive immune systems in prokaryotes are known to behave as selfish mobile elements. In the case of a system loss, the endonuclease enzyme tends to persist in the cytoplasm for a longer period of time compared to the protective methyltransferase, leading to the restriction of the genomes [30]. Thus, R–M systems are stably maintained in genomes as addictive selfish modules causing a strong dependency on the presence of the protective methyltransferase. In addition, they also tend to propagate efficiently by lateral gene transfers [31]. Recently, a new class of selfish mobile element has been evidenced in the *Bodo saltans*

Figure 1



Diversity of mobile genetic elements found in Giant virus genomes. The heat-map represents the maximum number of copies of each family of mobile elements identified in each viral lineage. The phylogeny is a schematic consensual tree obtained with conserved viral core genes supporting the monophyly of the group. Please note that Pandoraviridae, Mesomimiviridae Aquavirinae and Megavirinae are not actually recognized as families by the International Committee on the Taxonomy of Viruses (ICTV).