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50-plus years of fungal viruses

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ABSTRACT

Mycoviruses are widespread in all major taxa of fungi. They are transmitted intracellularly during cell division, sporogenesis, and/or cell-to-cell fusion (hyphal anastomosis), and thus their life cycles generally lack an extracellular phase. Their natural host ranges are limited to individuals within the same or closely related vegetative compatibility groups, although recent advances have established expanded experimental host ranges for some mycoviruses. Most known mycoviruses have dsRNA genomes packaged in isometric particles, but an increasing number of positive- or negative-strand ssRNA and ssDNA viruses have been isolated and characterized. Although many mycoviruses do not have marked effects on their hosts, those that reduce the virulence of their phytopathogenic fungal hosts are of considerable interest for development of novel biocontrol strategies. Mycoviruses that infect endophytic fungi and those that encode killer toxins are also of special interest. Structural analyses of mycoviruses have promoted better understanding of virus assembly, function, and evolution.

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Introduction and historical highlights

Knowledge of fungal viruses (mycoviruses) has expanded exponentially during the past 53 years, since the first definitive report of viruses infecting the cultivated button mushroom *Agaricus bisporus* (Hollings, 1962). A perception that all mycoviruses are cryptic dsRNA viruses has substantially changed as we have learned more about their genome diversity and potential impacts on their fungal hosts. In the age of a catastrophic Ebola outbreak, it is refreshing to write instead about mycoviruses and their potential benefits to humans; yes, not all viruses are evil, and some viruses may even enhance the value, beauty, or health of their hosts (Kernbauer et al., 2014; Lesnaw and Ghabrial, 2000). Mycoviruses in particular could conceivably be exploited for biological control of their natural fungal hosts that are pathogenic for plants. In the past, such applications of mycoviruses were markedly curtailed by technical difficulties in gaining an insight into their biology and structure, but these limitations have been decreasing with the advent of new research approaches (Dawe and Nuss, 2013; Xie and Jiang, 2014).

The economically important dieback disease of *A. bisporus*, a basidiomycete, was first identified in 1948 in a mushroom house owned by the La France brothers of Pennsylvania (Sinden and Hauser, 1950). The disease hence was called La France disease, and similar diseases were reported soon afterward from Europe, Japan, and Australia. In 1962, Hollings observed and isolated at least three types of virus particles from the sporophores of diseased mushrooms and demonstrated disease transmission to symptomless mushrooms by the isolated particles, marking the dawn of modern mycovirology. There were, of course, prior clues to the existence of mycoviruses, including the discovery in 1959 of the transmissible disease of *Helminthosporium* (*Cochliobolus*) *victoriae*, the filamentous ascomycete that causes Victoria blight of oats and other grains (reviewed by Ghabrial et al. (2013)). It is important to note, however, that despite their relatively recent discovery, fungal viruses are believed to be of ancient origins.

The discovery that viral double-stranded (ds)RNA was responsible for the interferon-inducing activities of culture filtrates from several species of ascomycetous molds in genus *Penicillium*, including *Penicillium chrysogenum*, greatly stimulated the search for mycoviruses and reflected the economic and medical importance of fungi in the 1960s (Ellis and Kleinschmit, 1967; Kleinschmit et al., 1964; Lampson et al., 1967). Both the particles and genomic dsRNAs of these Penicillium viruses are potent stimulators of interferon production in animals (Buck et al., 1971). Penicillium chrysogenum virus (PcV), the only known mycovirus to infect *P. chrysogenum*, has now been well characterized (Castón et al., 2013; Jiang and Ghabrial, 2004). The discovery of PcV particles in many *P. chrysogenum* strains used for industrial production of penicillin raised concerns about the stability of these strains. *P. chrysogenum* has been considered asexual for more than 100 years, and in the absence of sexual reproduction, it has been difficult to improve penicillin yield and strain stability. Recently, however, with knowledge of mating-type (MAT) gene organization, it has been possible to induce a sexual cycle, yielding meiotic ascospores of *P. chrysogenum* (Böhm et al., 2013). Evidence of recombination was obtained and the identified heterothallic sexual cycle was used to generate offspring with novel combinations of traits relevant to penicillin production. Because mycoviruses with possible exception of mitoviruses are reportedly eliminated from some higher ascomycetes by sexual reproduction (Khalifa and Pearson, 2013; McFadden et al., 1983; Xie et al., 2006), some of the ascospore-derived progenies of *P. chrysogenum* are likely to be virus-free, thus potentially improving strain stability.

The discovery of toxin-secreting strains of the ascomycetous yeast *Saccharomyces cerevisiae*, and their phenotypic association with the presence of dsRNA viruses (Bevan et al., 1973), marked the beginning of research into yeast virology in the early 1970s. It was then shown that certain yeast strains secrete protein toxins that are lethal to sensitive strains. The toxin-secreting strains were designated “killer yeasts” and the secreted proteins, “killer toxins” (reviewed by Schmitt and Breinig (2006) and Wickner et al. (2013)). Shortly after this discovery, it became apparent that toxin-producing killer strains are not limited to *S. cerevisiae*, but are also found among other yeast and fungal taxa, including *Hanseniaspora uvarum*, *Ustilago maydis*, and *Zygosaccharomyces bailii* (Park et al., 1996; Schmitt and Neuhausen, 1994). The killer phenotype is in some cases associated with dsRNA mycoviruses but can also be encoded by linear dsDNA plasmids (in *Kluyveromyces lactis* and *Pichia acacia*) or chromosomally (in *Williopsis californica* and *Pichia farinose*). The killer toxins from some yeast and smut strains are encoded by satellite dsRNAs, which are dependent on helper dsRNA viruses from family *Totiviridae* for replication and encapsidation. Although no satellite dsRNAs have been reported in association with virus infection of the filamentous ascomycete *H. victoriae* (Ghabrial and Nibert, 2009), the secreted protein toxin victoriocin, encoded by host chromosomal gene *vin*, is structurally similar to killer toxin-encoding genes (de Sá et al., 2010a, 2010b). Establishing that secreted killer toxins are expressed as preprotoxins has substantially strengthened our knowledge in many areas of biology and provided deeper understanding of essential cellular mechanisms such as posttranslational processing along the secretory pathway.

Fungal viruses are often associated with symptomless infections of their hosts. They are not known to have natural vectors (e.g., arthropods or annelids), are commonly transmitted horizontally in nature by intracellular means (hyphal anastomosis), and are transmitted vertically in nature by disseminating spores (mitotic and sometimes meiotic). Thus, although lacking an extracellular phase to their life cycles, they nevertheless have efficient means for both horizontal and vertical transmission and are clearly very successful, being prevalent in all major taxa of fungi. Estimates of mycovirus incidence suggest that 30–80% of fungal species may be infected (Ghabrial and Suzuki, 2009).

Mycoviruses are of common occurrence in endophytic fungi (fungal endosymbionts of plants), with potentially mutualistic roles in the complex interactions between the two organisms (Bao and Roossinck, 2013; Herrero et al., 2009, 2011). For example, mycoviruses might represent mobile elements that afford their partners greater flexibility for rapid adaptation, a promising trait during environmental changes. Greater understanding of the viruses of fungal endophytes may therefore be helpful for practicing sustainable agriculture, particularly against the backdrop of changing global climate. Moreover, recent phylogenetic studies

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