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Hytrosaviruses: current status and perspective

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Salivary gland hytrosaviruses (SGHVs) are entomopathogenic dsDNA, enveloped viruses that replicate in the salivary glands (SGs) of the adult dipterans, *Glossina* spp (GpSGHV) and *Musca domestica* (MdSGHV). Although belonging to the same virus family (*Hytrosaviridae*), SGHVs have distinct morphologies and pathobiologies. Two GpSGHV strains potentially account for the differential pathologies in lab-bred tsetse. New data suggest incorporation of host-derived cellular proteins and lipids into mature SGHVs. In addition to within the SGs, MdSGHV undergoes limited replication in the corpora allata, potentially disrupting hormone biosynthesis, and GpSGHV replicates in the milk glands providing a transmission conduit to progeny tsetse. Whereas MdSGHV is a potential biocontrol agent, the vertically transmitted GpSGHV is unsuitable for tsetse vector control but does jeopardize tsetse mass rearing.

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Introduction

Hytrosaviruses (SGHVs; *Hytrosaviridae* family) are classified into two genera, Glossinavirus and Muscavirus, that infect the hematophagous tsetse fly (*Glossina* spp.) and the filth-feeding housefly (*Musca domestica*), respectively [1]. SGHVs virions have large dsDNA genomes and form non-occluded, enveloped and rod-shaped virions. The two genera have only one type species each, *Glossina pallidipes* salivary gland hypertrophy virus (GpSGHV) and *Musca domestica* SGHV (MdSGHV). SGHVs are detected exclusively in adults of the dipterans, where they primarily replicate in the salivary glands (SGs), and induce diagnostic salivary gland hypertrophy (SGH) symptoms (Figure 1). Flies with overt SGH symptoms are often infertile, presumably due to virus infection/transcription in non-SG (reproductive) tissues [2•]. The MdSGHV and two GpSGHV lineages isolated from Ugandan and Ethiopian tsetse flies have been sequenced [3••]. A tentative *Hytrosaviridae* family member is a virus infecting the phytophagous syrphid fly, *Merodon equestris*. Reports of SGH-like symptoms in the male accessory gland filaments of a braconid wasp [4] suggest the existence of other SGHVs whose discovery is potentially hindered by the covert, chronic, and endemic viral infections [5].

Morphology and composition

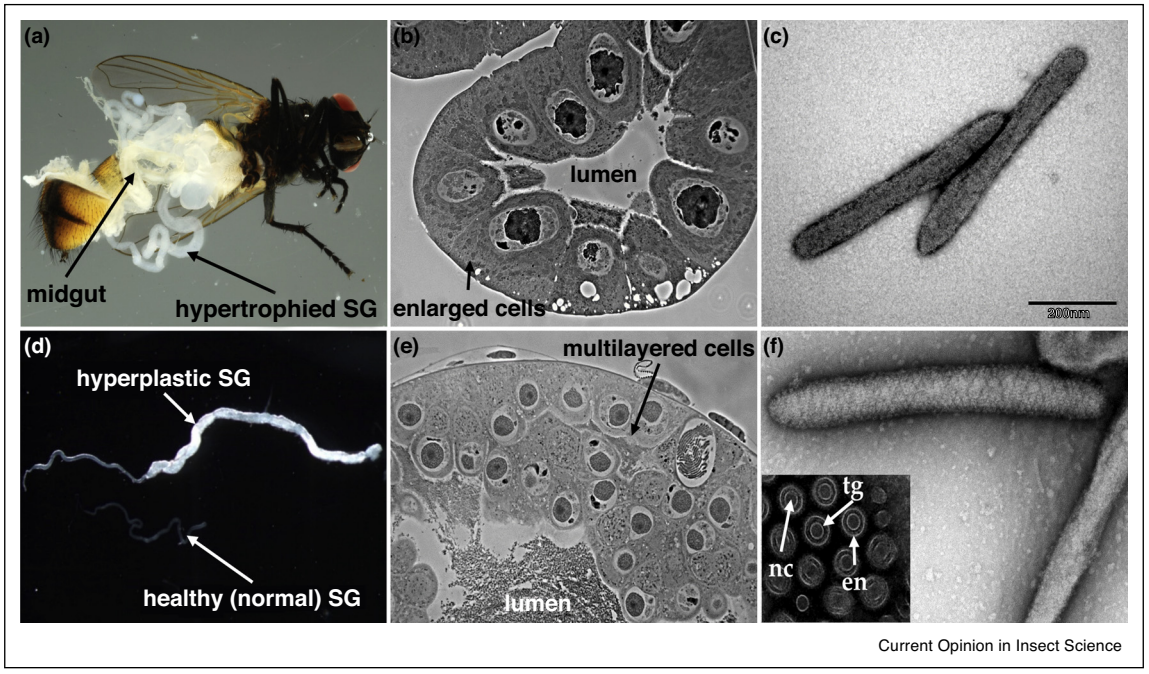
Virion components

The morphological, pathobiological and genomic properties (Figure 1) shared by SGHVs resulted in their classification into the *Hytrosaviridae* family. GpSGHV virions measure 50 × 1000 nm and contain a thin, dense, central nucleocapsid core encasing the 190 kb superhelical dsDNA viral genome. The outer surface of GpSGHV is studded with helical polymeric structures (13 nm long; 15 nm periodicity) composed of viral and host-derived proteins [6]. Underlying the viral envelope is a 10 nm thick proteinaceous tegument and a nucleocapsid core (4 nm in diameter). GpSGHV particles are fragile, which possibly accounts for their low viral infectivity (see Section *Symptomology, pathogenesis, and viral latency*). Compared to GpSGHV, MdSGHV virions are smaller (50 × 650 nm; 124 kb genome) and contain regularly spaced braided, bead-like surface projections. MdSGHV particles are more stable than those of GpSGHV. The unsequenced SGHV detected in the *M. equestris* is morphologically similar to MdSGHV in that its enveloped virions are 500–600 nm in length by 50–50 nm in diameter.

Structural viral proteins

The rod-shaped SGHV structural complex contains a blend of viral and host proteins. Proteomics of nucleocapsid and envelope fractions extracted from gradient-purified GpSGHV virions identified 57 proteins compared to 29 structural proteins encoded by MdSGHV. Of the GpSGHV proteins, 10, 15, and 20 proteins belong to the envelope, nucleocapsid, and tegument matrix, respectively [6]. Additionally, 12 virus-encoded proteins detected in intact GpSGHV virions were not detectable

Figure 1



(a) Light micrographs of hypertrophied salivary glands (SGs) dissected from *Musca domestica.* **(b)** MdSGHV-induced cellular hypertrophy in housefly SGs. **(c)** Structural features of MdSGHV particles. **(d)** Hyperplastic SGs of tsetse. **(e)** GpSGHV-induced hyperplasia in tsetse SGs. **(f)** TEM micrographs showing the main structural features of MdSGHV GpSGHV particle. Inset in Panel F shows the nucleocapsid core (nc), tegument (tg) and envelop (en).

in the fractionated virions, implying that they are non-structural proteins. Both the GpSGHV-Uga and GpSGHV-Eth isolates contained almost identical structural proteins [3••]. Comparisons between SDS-PAGE gel profiles of gradient-purified GpSGHV [7] and MdSGHV [8] revealed unique and shared bands in the MdSGHV nucleocapsid and envelope fractions, potentially representing tegument proteins.

Recent comprehensive annotation of GpSGHV peptides [3,6] revealed many homologs to structural proteins from other insect viruses (see Table 1 for detailed annotations). Notable nucleocapsid structural proteins included homologs involved in viral DNA assembly [9] and encapsidation [10], chromosomal structural positioning [11], and protein turnover during late viral infection [12]. Homologs to structural tegument proteins included proteins involved in PM disruption to initiate infection [13], nucleocapsid egress from virogenic stroma [14], and hijacking of the host cell ubiquitin machinery [15]. Notable envelope structural proteins included homologs to proteins essential for oral infection [13], viral replication and late gene expression [16], correct virus assembly [17], and morphogenesis of infectious virions [18]. Proteins that could not be associated with the structural components were assigned as infected, cell-specific viral proteins (ICSVPs) [3••]. Notable ICSVPs included homologs to proteins essential for viral DNA replication [16,19], late and very late viral transcription [16], nucleocapsid envelopment [14], and terminal host liquefaction [20]. Many of GpSGHV structural proteins had homologs in MdSGHV (Table 1; see also Ref. [21•••]). For example, the abundant tegument gene GpSGHV-Eth051 [3••] is homologous to the MdSGHV086. Immunogold labeling localized MdSGHV086 on the outer coat of nucleocapsid; this matrix protein potentially mediates the egress of MdSGHV nucleocapsid through the nuclear pore complex and in the envelopment of MdSGHV nucleocapsids (Figure 2).

In addition to virally encoded proteins, GpSGHV particles harbor at least 50 host-derived cellular proteins, of which ~50% were detected in the tegument [6]. At least 13 of these proteins are potentially incorporated into the virions, and their homologies to animal viruses imply that they served specific and auxiliary roles in viral morphogenesis [6]. Corresponding data on the MdSGHV are unavailable; analysis LC–MS/MS data was restricted to the comparisons to the viral genome. However, the viral envelope, derived from cytoplasmic envelopment process, predicts a similar incorporation of a complex of host proteins and lipids into all SGHVs.