## ABSTRACT

**Background:** Hytrosaviruses (SGHVs; Hytrosaviridae family) are double-stranded DNA (dsDNA) viruses that cause salivary gland hypertrophy (SGH) syndrome in flies. Two structurally and functionally distinct SGHVs are recognized; Glossina pallidipes SGHV (GpSGHV) and Musca domestica SGHV (MdSGHV), that infect the hematophagous tsetse fly and the filth-feeding housefly, respectively. Genome sizes and gene contents of GpSGHV (~ 190 kb; 160-174 genes) and MdSGHV (~ 124 kb; 108 genes) may reflect an evolution with the SGHV-hosts resulting in differences in pathobiology. Whereas GpSGHV can switch from asymptomatic to symptomatic infections in response to certain unknown cues, MdSGHV solely infects symptomatically. Overt SGH characterizes the symptomatic infections of SGHVs, but whereas MdSGHV induces both nuclear and cellular hypertrophy (enlarged non-replicative cells), GpSGHV induces cellular hyperplasia (enlarged replicative cells). Compared to GpSGHV's specificity to Glossina species, MdSGHV infects other sympatric muscids. The MdSGHV-induced total shutdown of oogenesis inhibits its vertical transmission, while the GpSGHV's asymptomatic and symptomatic infections promote vertical and horizontal transmission, respectively. This paper reviews the coevolution of the SGHVs and their hosts (housefly and tsetse fly) based on phylogenetic relatedness of immune gene orthologs/paralogs and compares this with other virus-insect models.

**Results:** Whereas MdSGHV is not vertically transmitted, GpSGHV is both vertically and horizontally transmitted, and the balance between the two transmission modes may significantly influence the pathogenesis of tsetse virus. The presence and absence of bacterial symbionts (Wigglesworthia and Sodalis) in tsetse and Wolbachia in the housefly, respectively, potentially contributes to the development of SGH symptoms. Unlike MdSGHV, GpSGHV contains not only host-derived proteins, but also appears to have evolutionarily recruited cellular genes from ancestral host(s) into its genome, which, although may be nonessential for viral replication, potentially contribute to the evasion of host's immune responses. Whereas MdSGHV has evolved strategies to counteract both the housefly's RNAi and apoptotic responses, the housefly has expanded its repertoire of immune effector, modulator and melanization genes compared to the tsetse fly.

**Conclusions:** The ecologies and life-histories of the housefly and tsetse fly may significantly influence coevolution of MdSGHV and GpSGHV with their hosts. Although there are still many unanswered questions regarding the pathogenesis of SGHVs, and the extent to which microbiota influence expression of overt SGH symptoms, SGHVs are attractive 'explorers' to elucidate the immune responses of their hosts, and the transmission modes of other large DNA viruses.



**Keywords:** Apoptosis; Glossina spp.; Glossinavirus; Hytrosaviridae; Musca domestica; Muscavirus; RNAi; Symbionts; miRNA.