Iridoviruses of Invertebrates

T Williams, Instituto de Ecología A.C., Xalapa, Mexico

Glossary

Circular permution Genome is a linear molecule of DNA with different terminal sequences at the population level. Physical maps of such genomes are circular.
Covert infection A sublethal infection that causes no obvious changes in the appearance or behavior of the host.
Cytopathic effect Alteration in the microscopic appearance of cultured cells following virus infection.
MCP Major capsid protein. A highly conserved structural polypeptide of *c.* 50 kDa that represents about 40% of the total protein content of the virion.
Patent infection Invertebrates that display iridescent hues due to an abundance of virus particles in crystalline arrays in infected cells.

Introduction

Invertebrate iridescent viruses (IIVs) (aka invertebrate iridoviruses) are icosahedral particles of approximately 120–200 nm in diameter that infect invertebrates, mostly insects, in damp or aquatic habitats. These viruses cause two types of disease: one patent and the other covert (inapparent). An abundance of virus particles in the cells of patently infected insects causes them to develop an obvious iridescent color that typically ranges from violet, blue, green, or orange. Patent disease is usually fatal in the larval or pupal stages. In contrast, covert infections are not lethal; covertly infected insects appear healthy and may develop to the adult stage and reproduce. Interest in these viruses has been limited by the perception that they have little potential as biological control agents against insect pests. However, there is now growing awareness of the potential impact of sublethal IIV disease on the dynamics of insect populations, including insect vectors of medical importance worldwide.

History

Originally discovered in 1954 infecting soil-dwelling populations of cranefly larvae (*Tipula paludosa*) in England, IIVs were subsequently reported in insects and other invertebrates worldwide. Detailed electron microscope observations in the late 1960s and early 1970s confirmed the icosahedral nature of the particle and revealed a complex ultrastructure including an internal lipid membrane and an external fringe of fibrils extending from the capsid of certain isolates. Serological relationships among IIVs and with iridoviruses from vertebrates were revealed during the 1970s and the genome of IIV-6 was shown to be circularly permuted and terminally redundant in 1984. Abundant covert IIV infections in insect populations were detected using molecular techniques and comparative genetic studies broadly supported previous serological findings on the relationships among these viruses in the 1990s. High-resolution ultrastructural studies in 2000 built on the previous model and the first complete genome of an IIV was sequenced in 2001.

Classification

IIVs are currently assigned to one of two genera in the family based on particle size and genetic characteristics. Small IIVs with dehydrated particle sizes in ultrathin section typically around 120 nm diameter have been isolated from several different orders of insects and terrestrial isopods and are assigned to the genus *Iridovirus* (**Table 1**). Due to the limited genome sequence data available, only two IIVs have been assigned species status, *Invertebrate iridescent virus 1* (IIV-1) and *Invertebrate iridescent virus 6* (IIV-6), that is the type species of the genus. Tipula iridescent virus and chilo iridescent virus are recognized synonyms of each of these names, respectively. An additional 11 viruses are presently considered as tentative species in the genus. The viruses of this genus can be further divided into three distinct complexes based on genetic and serological characteristics: one large complex containing IIV-1 and at least nine other IIVs, and two smaller complexes, one containing IIV-6, and the other containing IIV-31 and an IIV from a beetle (*Popillia japonica*).

The genus *Chloriridovirus* is comprised of a single species, *Invertebrate iridescent virus 3* (IIV-3), with a particle size of ~180 nm diameter in ultrathin section, isolated from a mosquito. There are a great many additional records of iridoviruses from invertebrate hosts but these have not been characterized.

Geographical Distribution

IIVs have been observed infecting invertebrates in tropical and temperate regions on every continent except Antarctica. A number of marine invertebrates have also been reported as

Table 1 Classification of iridoviruses isolated from invertebrates

Genus, virus (alternative name)	*Abbreviation*	*Host species (order)*[a]	*Location*	*Accession numbers*
Iridovirus				
Invertebrate iridescent virus 1 (Tipula iridescent virus)	IIV-1 (TIV)	*Tipula paludosa* (D)	UK	M33542, M62953
Invertebrate iridescent virus 6 (Chilo iridescent virus)	IIV-6 (CIV)	*Chilo suppressalis* (L)	Japan	AF303741, NC_003038
Anticarsia gemmatalis iridescent virus[b]	AGIV	*Anticarsia gemmatalis* (L)	USA	AF042343
Invertebrate iridescent virus 2[b]	IIV-2	*Sericesthis pruinosa* (C)	Australia	AF042335
Invertebrate iridescent virus 9[b]	IIV-9	*Wiseana cervinata* (L)[c]	New Zealand	AF025774, AY873793
Invertebrate iridescent virus 16[b]	IIV-16	*Costelytra zealandica* (C)	New Zealand	AF025775, AY873794
Invertebrate iridescent virus 21[b]	IIV-21	*Helicoverpa armigera* (L)[d]	Malawi	
Invertebrate iridescent virus 22[b]	IIV-22	*Simulium variegatum* (D)	UK	AF042341, M32799
Invertebrate iridescent virus 23[b]	IIV-23	*Heteronychus arator* (C)	South Africa	AF042342
Invertebrate iridescent virus 24[b]	IIV-24	*Apis cerana* (Hy)	Kashmir	AF042340
Invertebrate iridescent virus 29[b]	IIV-29	*Tenebrio molitor* (C)	USA	AF042339
Invertebrate iridescent virus 30[b]	IIV-30	*Helicoverpa zea* (L)	USA	AF042336
Invertebrate iridescent virus 31[b]	IIV-31	*Armadillidium vulgare* (Is)[e]	USA	AF042337, AJ279821, AF297060
Chloriridovirus				
Invertebrate iridescent virus 3	IIV-3	*Ochlerotatus (Aedes) taeniorhynchus* (D)	USA	AJ312708

[a]Insect orders Coleoptera (C), Diptera (D), Homoptera (H), Hymenoptera (Hy), Lepidoptera (L), and terrestrial isopods (Is) (Crustacea).
[b]Tentative member.
[c]Also isolated from sympatric insect species *Witlesia sabulosella* (L) and *Opogonia* sp. (C).
[d]Also isolated from *Lethocerus colombiae* (H) in Lake Victoria, Uganda, but may have been contaminated.
[e]Also isolated from *Porcellio dilatatus* and probably several other species of terrestrial isopods.

hosts to iridoviruses. Humidity appears to be the principal factor limiting the distribution of these viruses. Records of IIV infections are most common in aquatic or soil-dwelling arthropods during periods of rainfall and absent in species that inhabit arid or desiccated habitats.

Host Range and Virus Propagation

IIVs replicate in many types of insect cells and may even replicate in reptilian cells *in vitro*. Host range *in vivo* depends very much on the route of infection. Most IIVs show a remarkably broad host range when the inoculum is injected compared to a reduced host range following oral administration of inoculum. For example, injection of particles of IIV-6 results in patent infections in species from all major insect orders and a number of other arthropods isopods and a centipede. Other IIVs, such as IIV-3, IIV-16, or IIV-24, appear restricted to one or two closely related host species. Certain IIVs are capable of infecting multiple host species in their natural habitat, including IIV-9 that infects soil-dwelling species of Lepidoptera and Coleoptera in New Zealand, and IIV-31 that infects several species of terrestrial isopods in the USA. IIVs are also capable of replication in host species that do not develop signs of disease, but the range of species susceptible to such asymptomatic infections is largely unknown.

Virus propagation *in vitro* is most readily achieved in cell lines from dipteran (*Aedes aegypti*, *Ae. albopictus*, *Drosophila* DR1, DL2, etc.) and lepidopteran species (Sf-9, Sf-21, Cf-124, etc.), although recently, cell lines from species of Homoptera and Coleoptera have also been successfully used. Most IIVs can be grown in massive quantities in the standard laboratory host, *Galleria mellonella* (Lepidoptera: Pyralidae). The mosquito virus IIV-3 can only be produced *in vivo* in larvae of *Ochlerotatus taeniorhynchus*.

Properties of the Virion

IIV particles comprise an electron dense core of DNA and associated proteins, surrounded by a lipid membrane encased by an exterior protein capsid (**Figure 1**). Virions released by budding may have an additional outer envelope but this is not essential for infectivity. Detailed studies using cryo-electron microscopy and three-dimensional image reconstruction have examined particles of IIV-6 in closely packed quasi-crystalline hexagonal arrays with an interparticle distance of 40–60 nm. Particle diameter was calculated to be 162 nm along the two- and threefold axes of symmetry and 185 nm along the fivefold axis, considerably larger than the diameter in ultrathin section. The outer capsid is composed of trimeric capsomers, each approximately 8 nm diameter and 7.5 nm high, arranged in a pseudo-hexagonal array. A thin fiber projects radially from the surface of each capsomer that probably regulates interparticle distance, a key characteristic for the iridescence of infected hosts. At the base, the

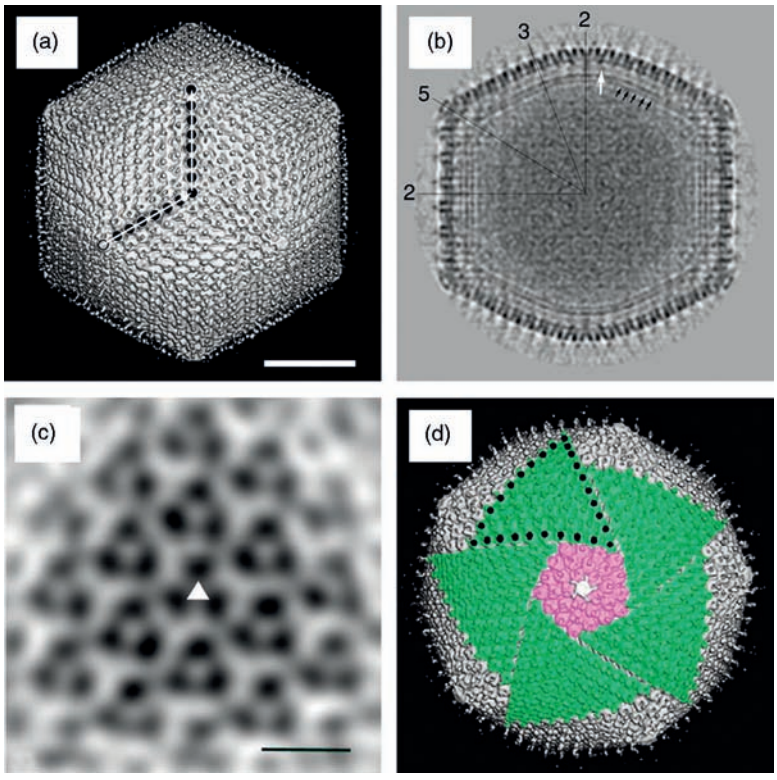

Figure 1 (a) 3-D reconstruction of an IIV-6 particle viewed down threefold axes of symmetry by cryoelectron microscopy. Circles indicate the position of capsomers along the h and k lattice used to calculate the triangulation number (*T*). The proximal end of surface fibers are visible, whereas the flexible distal ends have become lost during the reconstruction process (white bar = 50 nm applies to images (a)–(c)). (b) Central section of the reconstruction density map viewed along twofold axes indicating two-, three-, and fivefold axes of symmetry. A lipid bilayer is observed beneath the capsid shell (black arrows) with numerous connections to an additional shell (white arrow) beneath the outer shell. (c) Close-up view of the trimers comprising each capsomer shown as a planar section through a reconstruction density map viewed along threefold axes (triangle) (black bar = 10 nm). (d) Facets of capsid with five trisymmetrons (highlighted in green) arranged around one pentasymmetron (in pink). The central capsomer of the pentasymmetron (uncolored) is pentavalent. The edge of each trisymmetron comprises 10 capsomers (black dots). Reprinted by permission from Macmillan Publishers Ltd: Nature Structural Biology, Yan X, Olson NH, Van Etten JL, Bergoin M, Rossmann MG, Baker TS (2000) Structure and assembly of large lipid-containing dsDNA viruses. *Nature Structural Biology* 7: 101–103, copyright (2000).

interconnected capsomers form a contiguous icosahedral shell ~2.5 nm thick. The major capsid protein (MCP) exists externally as a noncovalent trimer and internally as a trimer linked by disulfide bonds. The capsomers are arranged into trisymmetron and pentasymmetron facets. Each particle consists of 20 trisymmetrons, composed of 55 capsomers, and 12 pentasymmetrons composed of 30 capsomers and one hexavalent capsomer of uncertain composition. Pentavalent capsomers are located at the vertices of the particle in the center of each pentasymmetron. This gives a total of 1460 capsomers + 12 pentavalent capsomers per particle. The triangulation number (T) is 147. Larger IIVs that infect mosquitoes and midges have larger trisymetrons, probably comprising 78 subunits giving a likely 1560 subunits per particle. A lipid bilayer, 4 nm thick, surrounds the DNA core, and is intimately associated with an additional inner shell beneath the fused layer of the capsid. Core and capsid polypeptides are likely interconnected by intermembrane proteins passing through the lipid layer. The core is a highly hydrated entity in which the DNA–protein complex appears to be arranged in a long coiled filament of some 10 nm diameter.

IIVs are structurally complex: one-dimensional PAGE resolves 20–32 polypeptides with weights typically from 11 to 200 kDa. Much of the polypeptide diversity of IVs appears to be associated with the core and lipid membrane. At least six polypeptide species are associated with the DNA within the core, the major component being a 12.5 kDa species in IV-6. The MCP comprises about 470 amino acids (~50 kDa) and represents 40–45% of the total particle polypeptide.

Properties of the Genome

Each IIV genome is comprised of a linear molecule of DNA that ranges in size from 140 to 210 kbp, and is circularly permuted and terminally redundant. Circular permution means that the terminal sequences differ for each genome in

a population, whereas terminal redundancy means that part of the sequence at one end of the DNA molecule is repeated at the other end. For example, if a complete genome is represented by the numbers 0–9, the DNA molecules from individual virus particles may be represented by the following combinations: 012345678901, 234567890123, 4567890123456, etc., where terminal redundancy is indicated by the underlined numbers. In IIV-6, the degree of terminal redundancy has been estimated as 12% and the genome contains six origins of replication.

The IIV genome is either not methylated, or methylated at very low or undetectable levels. In contrast, high levels of methylation of cytosine residues are seen in virtually all vertebrate iridoviruses. Currently, only two IIV genomes have been sequenced in their entirety: IIV-3 and IIV-6. The genome of IIV-6 is 212 kbp (unique portion) with 28.6% G+C content and comprises 468 open reading frames (ORFs), of which 234 are nonoverlapping. The genome of IIV-3 is 191 kbp (unique portion) with a 48% G+C content and comprises 453 ORFs, of which 126 are nonoverlapping. No collinearity is observed between the genomes of IIV-3 and IIV-6.

Core IIV genes include those involved in (1) replication, including DNA polymerase (037L), RNA polymerase II (α-subunit 176R, β-subunit 428L), Rnase III (142R), a helicase (161L), and a DNA topoisomerase II (045L); (2) nucleotide metabolism, such as ribonucleotide reductase (α-subunit 085L, β-subunit 376L), dUTPase (438L), thymidylate synthase (225R), thymidylate kinase (251L), and thymidine kinase (143R); and (3) other proteins of known function including IAP inhibitor of apoptosis (157L, 193R), PCNA (436R), and the MCP (274L).

Other notable putative genes identified in IIV-6 include an NAD+-dependent DNA ligase (205R) and a putative homolog of sillucin (160L), a cysteine-rich peptide antibiotic. The promoter regions of the MCP and DNA polymerase genes have been located to essential sequences at 29–53 and 6–27 positions upstream of the transcriptional start site, respectively (**Figure 2**). An ORF (100L) has been detected in IIV-6 with truncated homology to the nuclear polymerizing (ADP-ribosyl) transferase from eukaryotic organisms. Interestingly, the large subunit of the IIV-6 ribonucleotide reductase appears to contain an intein, a form of selfish genetic element that removes itself from the protein by post-translational autocatalytic splicing. Genes unique to IIV-3 include two putative transmembrane proteins, a protein similar to fungal DNA polymerase, and a protein similar to a fungi RNA Pol II subunit.

IIVs have been shown to have extensive regions of repetitive DNA that account for 20% (IIV-3) to over 25% (IIV-9) of the genome. The coding function of these regions is unknown although transcription of these regions has been detected late in the infection cycle. The pattern of repetitive DNA in the genome of IIV-6 is complex and involves boxes of tandem repeat sequences and others with a number of different interdigitated repeat sequences of variable size and homology.

Replication

The model for iridovirus replication is that of frog virus 3 (FV-3). Virions display cytotoxic properties and are capable of nongenetic reactivation. Like all other members of the family, IIVs do not replicate at temperatures above 30 °C.

Evolution

Iridoviruses are members of a monophyletic clade of large, nucleocytoplasmic DNA viruses that includes the families *Poxviridae, Phycodnaviridae*, *Asfarviridae* and the recently discovered giant icosahedral mimivirus from an ameba. The clade shares a total of 41 ancestral genes including structural components, and those involved in DNA packaging, replication, transcription and RNA modification including subunits of RNA polymerase and transcription factors, many of which appear to have been acquired from eukaryotic host cells.

Sequence comparisons of the virus-encoded δ DNA polymerase and MCP indicated putative evolutionary relationships between IIVs and ascoviruses of lepidopteran insects. Homologs to about 40% of the proteins encoded by *Spodoptera frugiperda ascovirus 1a* are found in IIV-6 with lower percentages seen among vertebrate iridoviruses, phycodnaviruses, and African swine fever virus (ASFV). Additional analyses based on *bro* genes (Baculovirus repeated ORFs), a multigene family of unknown function, support the conclusion that ascoviruses are more closely related to invertebrate iridoviruses than to vertebrate iridoviruses. Like IIVs, lepidopteran ascoviruses have very low oral infectivity but are highly infectious by injection and depend on parasitoid wasps for transmission. Structural similarities between iridoviruses and the allantoid particles of ascoviruses are not immediately apparent although molecular evidence indicates clear relationships between these viruses.

Signs and Characteristics of Disease

The principal sign of patent IV infection is the iridescent hues which arise from the paracrystalline arrangement of virus particles in host cells. Light is reflected from the surface of close packed particles and causes interference with incident light known as 'Bragg reflections'.

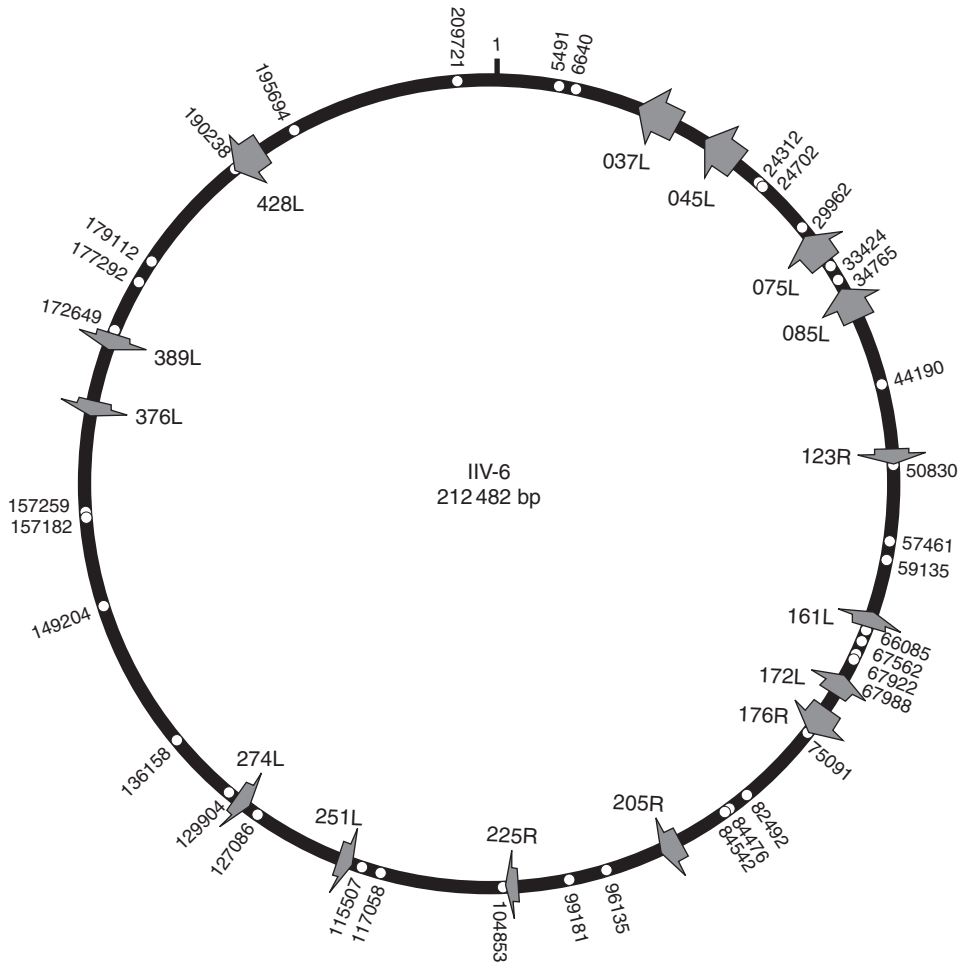

Figure 2 Genetic map of IIV-6. Position of selected ORFs (arrows) identified in the complete genome sequence of IIV-6 that encode the following putative proteins: DNA polymerase (037L), topoisomerase II (045L), ATPase (075L), ribonucleoside diphosphate reductase large subunit (085L), protein-tyrosine phosphatase (123R), helicase (161L), global transactivator homolog (172L), DNA-dependent RNA polymerase 1 (176R), DNA ligase (205R), thymidylate synthase (225R), thymidylate kinase (251L), major capsid protein (274L), ribonucleoside diphosphate reductase small subunit (376L), serine-threonine protein kinase (389L), DNA-dependent RNA polymerase 2 (428L). White dots accompanied by figures indicate the nucleotide positions of *Eco*RI cleavage sites. Reproduced from Jakob N, Darai G, and Williams T (2002) Genus *Iridovirus*. In: Christian T and Darai G (eds.) *Springer Index of Viruses*, Berlin: Springer, with kind permission of Springer Science and Business Media.

The small IIVs of the genus *Iridovirus* usually display violet, blue, or turquoise colors, whereas large IIVs from mosquitoes (genus *Chloriridovirus*) commonly display colors such as green, yellow, or orange. Purified pellets of IIVs also iridesce. Some isolates have unusually long external fibrils attached to the capsid and these isolates do not iridesce.

Covert infections have been detected in natural populations of blackflies (*Simulium variegatum*) and a mayfly (*Ecdyonurus torrentis*), and in laboratory populations of a mosquito (*Ae. aegypti*) and a lepidopteran (*G. mellonella*). Covert infections have been detected by polymerase chain reaction (PCR) amplification of the MCP gene, electron microscope observations, and insect bioassay techniques (**Figure 3**). Studies on IIV-6 in *Ae. aegypti* have revealed clear costs of covert infection including an increase in larval development time and reductions in adult body size, longevity, and fecundity. Overall the reproductive capacity of covertly infected mosquitoes is reduced by 22–50% compared to healthy mosquitoes, depending on the number of cycles of blood meals followed by oviposition.

Pathology

IIVs replicate extensively in most host tissues, especially the epidermis, muscles, fat body, nerves, hemocytes, and areas of the gut. IIV-1 caused the formation of epidermal

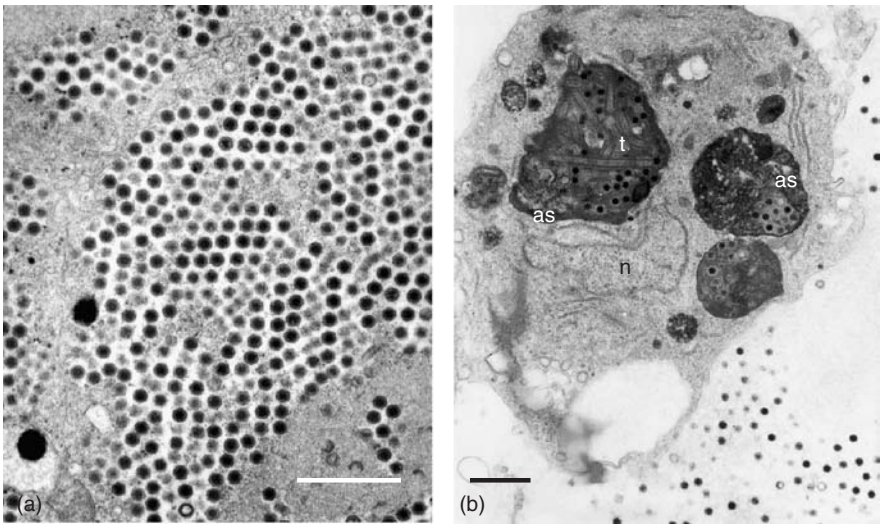

Figure 3 IIV particles in cytoplasm of cells from insects with patent or covert infection. (a) Arrays of closely packed particles of IIV-3 in an epidermal cell from a patently infected mosquito larva. Scale = 1 μm. (b) Low density of particles in a hemocyte from a covertly infected mayfly larva. Cells from covertly infected insects show the characteristic cytoplasmic virus assembly sites (as) close to the nucleus (n), and also the presence of tubular structures (t) likely to be aberrant forms of virus capsids. Scale = 1 μm. (a) Photo courtesy of J. J. Becnel. (b) Reproduced from Tonka T and Weiser J (2000) Iridovirus infection in mayfly larvae. *Journal of Invertebrate Pathology* 76: 229–231, with permission from Elsevier.

tumors in silkworm larvae but such pathology is not observed in other hosts. In mosquito larvae infected by IIV-3, the fat body, epidermis, imaginal disks, hemocytes, trachea, muscle, visceral nerves, gonads, and esophagus were infected but not the remaining gut or malpighian tubules. Individuals with patent infections that survive to pupate frequently show marked deformations of the pupa, particularly of the wing buds.

Pathological changes at the cellular level include cell rounding and the appearance of extensive areas of finely granulated material devoid of cell organelles, the cytoplasmic virus assembly sites. Marked contraction of the cells followed by cell detachment are also common cytopathic effects. Rapid cell–cell fusion is influenced by the multiplicity of infection in cells infected by IIV-6. A virion-associated protein appears to be responsible. The formation of numerous vesicles arising from blebbing of cell membranes followed by loss of cell adhesion and cell–cell fusion has also been observed in lepidopteran cells infected by IIV-1. Changes in the position and morphology of mitochondria have been reported.

Ecology

Ecological studies of IIVs are sparse, probably because the incidence of patent disease is typically very low. The majority of studies have used iridescence as the sole criterion for diagnosing infection, although PCR and insect bioassay have also been employed successfully to detect and quantify covert infections. Studies on backflies and Lepidoptera have indicated that there exists considerable genotypic variation in IIV populations such that individual insects collected at the same place and time may harbor genetically distinct variants.

Studies on transmission have been hindered because the route of infection is unknown or uncertain for most IIV–host systems. Cannibalism or predation of infected individuals involves the consumption of massive doses of particles and appears to be the principal mechanism of transmission in populations of mosquitoes, isopods, tipulids, mole crickets, and cannibalistic species of Lepidoptera. Hymenopteran parasitoids and entomopathogenic nematodes have been shown capable of transmitting IIV infections during the act of oviposition or host penetration, respectively. Survival of IIV-3 in mosquito populations appears to depend on alternating cycles of horizontal transmission between cannibalistic larvae and vertical transmission from adult female mosquitoes that acquire infection shortly before pupating. Horizontal transmission is also favored in high-density populations of some hosts wherein the frequency of aggressive encounters between conspecifics and the probability of wounding is greater than at low densities.

There is clear evidence of seasonality in many IIV–host associations due to seasonal fluctuations in precipitation and/or host densities. The persistence of IIV-6 in soil depends on moisture, whereas persistence in water is markedly affected by solar ultraviolet radiation.

Occasional epizootics of patent disease have been reported in lepidopteran species, *Helicoverpa zea* and *Anticarsia gemmatalis*, the cricket *Scapteriscus borellii*, as well as tipulid, mosquito, and blackfly larvae.

Economic Importance

IIVs have been observed to infect natural populations of major insect pests and numerous species of insect vectors of medical or veterinary importance (mosquitoes, midges, and blackflies). However, the low prevalence of patent infections and relatively broad host range of most IIVs means that these viruses are not considered as likely agents for programs of biological control. An IIV is believed to be responsible for periodically devastating populations of mopane worms (*Gonimbrasia belina*, Lepidoptera) that represent a multimillion dollar food industry in several southern African countries. Iridovirus infections are also associated with severe diseases and mass mortalities in oyster populations, but the relationship between these marine iridovirus and those infecting terrestrial and freshwater arthropods is unknown.

See also: Ascoviruses; Baculoviruses: General Features; Iridoviruses: General Features; Iridoviruses of Vertebrates.

Further Reading

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Iridoviruses: General Features

V G Chinchar, University of Mississippi Medical Center, Jackson, MS, USA
A D Hyatt, Australian Animal Health Laboratory, Geelong, VIC, Australia

Glossary

Anuran An amphibian of the order Salientia (formerly Anura or Batrachia) which includes frogs and toads. Also called, salientians.

Introduction

Members of the family *Iridoviridae*, hereafter referred to as iridovirids to distinguish them from members of the genus *Iridovirus*, are large (120–200 nm), double-stranded DNA viruses that utilize both the nucleus and the cytoplasm in the synthesis of viral macromolecules, but confine virion formation to morphologically distinct, cytoplasmic assembly sites. Virus particles display icosahedral symmetry but, unlike other virus families, infectious virions can be either nonenveloped (i.e., naked) or enveloped, although the latter show a higher specific infectivity. The viral capsid is composed primarily of the major capsid protein (MCP), a ~50 kDa protein that is highly conserved among all members of the family. An internal lipid membrane, that is essential for infectivity, underlies the capsid and encloses the viral DNA core. Approximately 30 virion-associated proteins have been identified by gel electrophoresis, but the functions of most of these proteins are unknown. The viral genome is linear, double-stranded DNA and ranges in size from 103 to 212 kbp, depending upon the viral species. As a likely consequence of its mode of packaging, viral DNA is terminally redundant and circularly permuted. The size of the repeat regions range from 5% to 50% of the genome and, like the genome size, appears to vary with the specific viral species.

Iridovirus Taxonomy

Members of the family *Iridoviridae* are classified into five genera, two of which infect invertebrates (*Iridovirus*, *Chloriridovirus*), and three that infect ectothermic vertebrates (*Ranavirus*, *Lymphocystivirus*, and *Megalocytivirus*). In addition to differences in host range, viruses within the three vertebrate iridovirus genera, with one known exception, contain highly methylated genomes in which every cytosine present within a CpG motif is methylated.