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Review

Viruses and Antiviral Responses of Nematodes

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Abstract

Nematodes are ubiquitous metazoans that occupy diverse ecological niches, exposing them to a wide range of viruses and positioning them as both viral hosts and vectors. Free-living nematodes, particularly *Caenorhabditis elegans* and *Caenorhabditis briggsae*, provide powerful genetic models for studying antiviral immune mechanisms. Natural infections with noda-like viruses have revealed powerful antiviral defense strategies in *Caenorhabditis* species, including RNA interference, the Intracellular Pathogen Response, Signal Transducers and Activators of Transcription (STAT)-like transcriptional regulation, terminal RNA uridylation, and structural barriers to viral entry and egress. These mechanisms demonstrate robust antiviral mechanisms independent of canonical interferon signaling while relying on conserved principles of viral RNA recognition, signal amplification, and coordinated transcriptional responses. Beyond free-living species, parasitic nematodes harbor a diverse and largely unexplored virome. Plant-parasitic nematodes host multiple RNA viruses and act as vectors for economically and agriculturally important plant pathogens, while animal-parasitic nematodes carry persistent viral infections that may influence the immune responses and disease outcomes of their animal hosts. Evidence for functional antiviral RNA interference in parasitic nematodes suggests partial conservation of immune mechanisms, although functional data remain limited. Together, these findings define current knowledge of viral infections and antiviral responses in nematodes and emphasize the need for deeper mechanistic studies, particularly in parasitic species, where the molecular basis of viral recognition and immune defense remains poorly characterized.

Keywords: nematodes; *Caenorhabditis elegans*; genetic models; RNA interference; immunity; virome; RNA viruses; viral RNA; viruses

1. Introduction

Nematodes are the most abundant metazoans on Earth, inhabiting nearly every ecological niche while spanning a wide range from free-living microbivores in soil and aquatic environments to obligate parasites of plants and animals [1]. This extraordinary diversity exposes them to a wide array of viruses, positioning nematodes as both viral hosts and vectors. The versatility of nematodes provides a powerful system for studying viral infection and transmission, host-pathogen interactions, and antiviral defense mechanisms [2].

A free-living nematode, *Caenorhabditis elegans* is a small soil-dwelling worm widely used as a model organism in molecular and genetic research. Its fully sequenced genome, well-characterized cell lineage, experimental tractability, and optical transparency allow precise visualization and manipulation of biological processes in a whole-organism context. These features, combined with ease of laboratory maintenance and conservation of many genes shared with humans, make *C. elegans* particularly well-suited for studying conserved molecular pathways, including immune responses [3,4].

In 2011, natural viral infections were discovered in *C. elegans* and the related species *Caenorhabditis briggsae*, providing a unique opportunity to study host-virus interactions under a natural infection route using the powerful genetic and molecular tools available in these model organisms [5]. These discoveries have transformed innate immune research, revealing novel antiviral defense strategies and highlighting the influence of host genetics, viral diversity, and the microbiome on infection outcomes [6,7,8,9,10,11].

Outside free-living species, parasitic nematodes have profound impacts on agriculture and human health and play important roles in viral transmission [12,13]. Plant-parasitic nematodes (PPNs) cause an estimated $157 billion in crop losses annually, posing a consistent threat to agricultural sustainability [14,15]. Several PPN genera, including *Xiphinema* and *Longidorus*, function as vectors for economically important plant viruses such as grapevine fanleaf virus and tomato black ring virus [16,17]. In humans, parasitic nematodes transmitted by insects such as *Brugia malayi* and *Onchocerca volvulus* cause filariasis diseases affecting around 51 million people worldwide, while soil-transmitted helminths (STHs) like *Strongyloides stercoralis* infect hundreds of millions [18,19,20]. Interestingly, recent work suggests that viral infections within parasitic nematodes can influence host immune responses, adding an additional layer of complexity to host–nematode–virus interactions [21,22].

In this review, we examine viral infections in nematodes from two complementary perspectives, considering nematodes both as viral hosts and as viral vectors. We focus

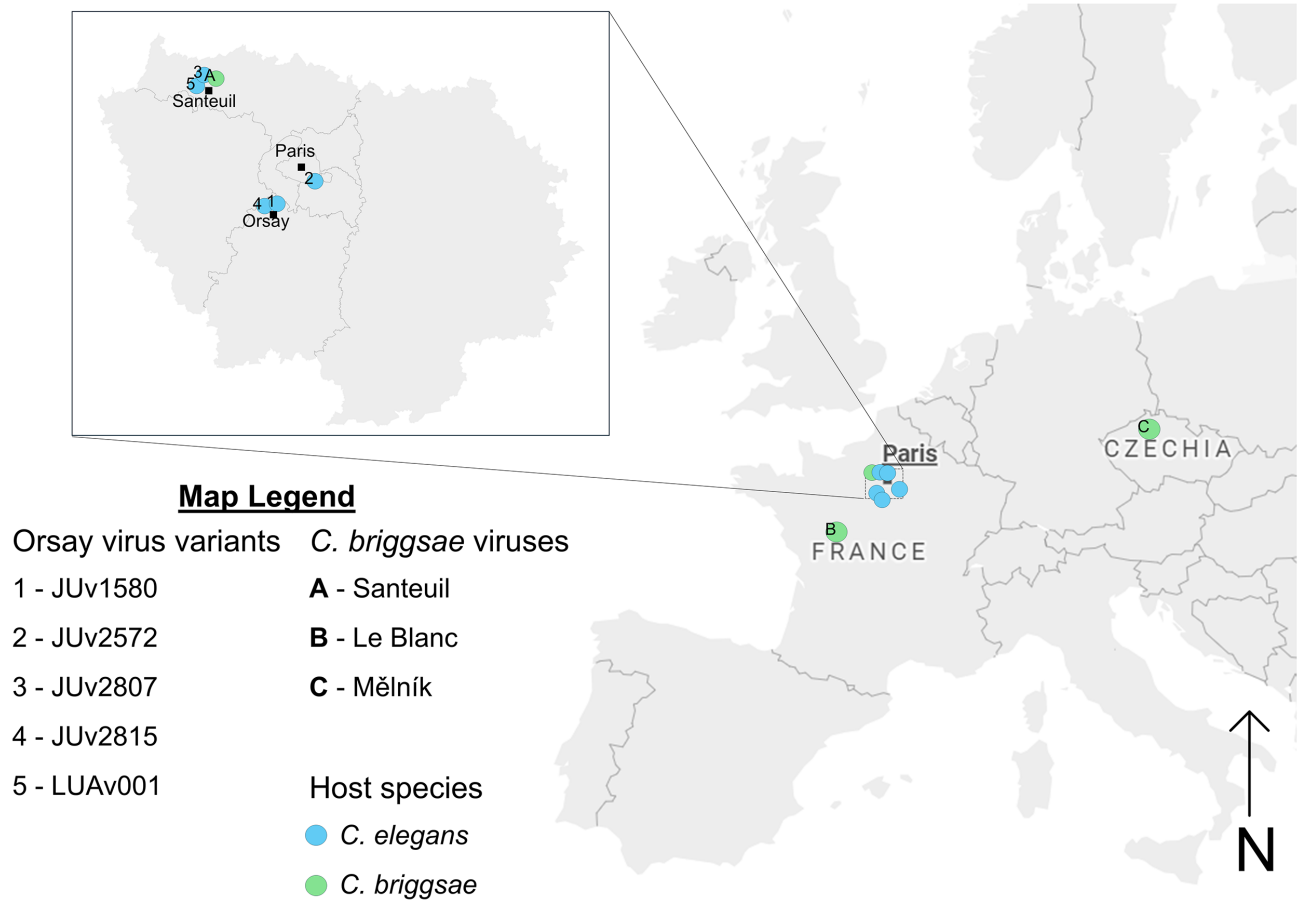

Fig. 1. Geographical illustration of natural viral isolates found in *Caenorhabditis* spp. in western and central Europe. Locations of natural viral discovery are organized by the species they were discovered in, with blue dots denoting a virus isolated from *C. elegans* and green dots denoting a virus isolated from *C. briggsae*. Numbers 1–5 highlight variants of Orsay virus found in wild *C. elegans* isolates and letters A–C denote Santeuil, Le Blanc, and Mělník viruses in *C. briggsae*. Figure made with Datawrapper.com.

on the molecular and genetic mechanisms governing antiviral defense in *C. elegans* and *C. briggsae*, alongside emerging insights into how pathogenic nematodes transmit and interact with viruses in plant and animal hosts. Together, these systems provide a powerful framework for uncovering conserved principles of viral infection and immunity across diverse biological contexts.

2. Viral Infections in *C. elegans*

Orsay virus is currently the only virus known to naturally infect *C. elegans*, with five variants identified to date [5,23]. It was first isolated from wild nematodes collected in an apple orchard near Orsay, France, from which it derives its name (Fig. 1) [5]. Orsay virus is a non-enveloped positive-sense single-stranded (+ssRNA) virus with a genome size of approximately 6.3 kb and is closely related to members of the *Nodaviridae* family (Table 1, Ref. [5,21,24,25,26,27,28,29,30,31,32,33,34,35,36]) [5,24]. Although it shares key features with nodaviruses, including icosahedral capsid architecture and genome organization, Orsay virus lacks the RNA silencing suppressor B2 commonly encoded by nodaviruses to counteract antiviral RNA interference (RNAi) [37].

The two-segment (bipartite) Orsay virus genome consists of RNA1 and RNA2 segments, which together encode four proteins [5,38]. RNA1 contains a single open reading frame (ORF) encoding the RNA-dependent RNA polymerase (RdRp), which first synthesizes a negative-sense antigenome that then serves as a template for production of new positive-sense viral genomes [5,39]. RNA2 contains two overlapping ORFs that give rise to three distinct proteins: a viral capsid protein (CP), a δ protein putatively involved in viral entry and exit, and a CP-δ fusion protein produced through ribosomal frameshifting [24,38,40]. Interestingly, the CP-δ fusion protein is incorporated into the virus capsid as a head fiber and may facilitate host cell entry [5,24,41]. Free δ protein aggregates alongside the terminal web, a cytoplasmic layer rich in actin and intermediate filaments (IFs) which anchor the microvilli in the polarized intestinal cells of *C. elegans*, potentially promoting terminal web reorganization and non-lytic viral egress (Fig. 2) [40,42,43].

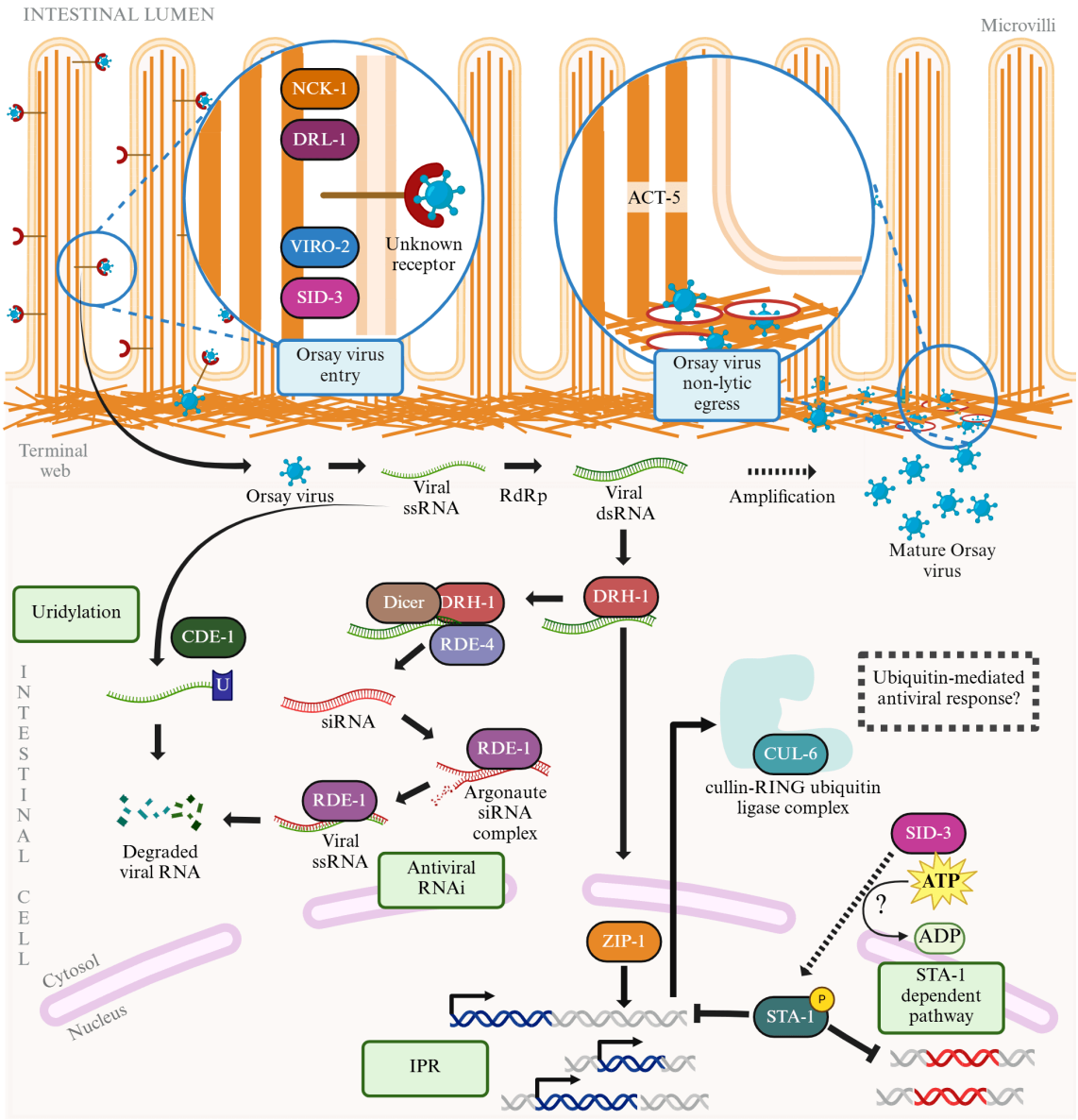

Fig. 2. Overview of Orsay virus infection in *C. elegans* and the antiviral response. Orsay virus enters intestinal cells by attaching to an unknown receptor, a process mediated by four identified host proteins. The antiviral response includes RNAi, IPR, STA-1, and 3' uridylation. Orsay virus exit into the intestinal lumen is non-lytic and involves reorganization of the terminal web. RNAi, RNA interference; IPR, Intracellular Pathogen Response. Figure made with BioRender.com.

Orsay virus is restricted to horizontal transmission via the fecal-oral route, with no evidence of vertical transmission [5]. Infection begins with ingestion of viral particles into the intestinal lumen, which are internalized by intestinal cells via an unknown receptor (Fig. 2) [25]. The virus shows strict tropism for the 20 intestinal cells of *C. elegans*, preferentially infecting the most anterior cells [5,25,44]. Under standard laboratory conditions, when animals are fed *Escherichia coli* strain OP50, infection is typically limited to one to six intestinal cells, as determined by immunofluorescence and FISH analyses [25,44]. However, exposure of *C. elegans* to naturally associated members of its microbiome significantly alters, and in many cases reduces Orsay virus infection [10]. This effect is not due to poor nutritional value of bacteria or virion degradation by bacteria [10].

Morphologically, Orsay virus infection leads to cytosolic liquefaction, formation of multimembrane bodies, nuclear degeneration, loss of gut granules, increased intestinal lumen size, and cell fusion [5,25,44,45]. Primary Orsay virus infection limits viral replication during subsequent infection with related Orsay virus strains, suggesting a cross-protective immune response [46]. At the end of the infection cycle, Orsay virus exits non-lytically into the lumen of the intestine and is excreted into the environment to initiate a new infection cycle in nearby feeding *C. elegans* (Fig. 2) [5].

Table 1. Overview of viruses found in soil-dwelling, plant parasitic, and animal parasitic nematodes.

Nematode species	Virus	Family	Genome organization			Tissue	Viral transfer	Refs.
			Structure and sense	Strands and size	Variants			
Viruses of free-living nematodes								
C. elegans	Orsay virus	NC*	RNA, bipartite, positive	Single, ~6.3 kb	5	Intestine	Horizontal	[5,24,25,26]
C. briggsae	Le Blanc virus	NC*	RNA, bipartite, positive	Single, ~6.5 kb	1			[25,27,28,29]
	Santeuil virus	NC*	RNA, bipartite, positive	Single, N/A	3			[5,25,29,30]
	Mělník virus	NC*	RNA, bipartite, positive	Single, N/A	1			[28,29]
Viruses of PPNs								
H. glycines (SCN)	Phlebovirus (ScPV)	*Bunyaviridae*	RNA, N/A, negative	Single, N/A	2	N/A	Vertical	[31]
	Tenuivirus (ScTV)	NC	RNA, multipartite, negative	Single, N/A	1			[31]
	Rhabdovirus (ScRV)	*Rhabdoviridae*	RNA, N/A, negative	Single, N/A	1			[31]
	Virus 5 (SbCNV-5)	*Flaviviridae*	RNA, N/A, positive	Single, N/A	1			[32]
	Socyvirus-1 (SbCNV-1)	*Nyamiviridae*	RNA, N/A, negative	Single, N/A	1			[31]
	Nyami-like virus (NLV)	*Nyamiviridae*	RNA, multipartite, negative	N/A	1			[33]
	Bunya-like virus (BLV)	NC	RNA, multipartite, negative	N/A	1			[33]
G. pallida (PCN)	Picorna-like virus (PLV)	NC	RNA, N/A, positive	N/A	1	N/A	N/A	[33]
	Potato cyst nematode rhabdovirus (PcRV)	*Rhabdoviridae*	RNA, N/A, negative	Single	1		Vertical	[34]
Viruses of APNs								
S. ceratophorum (EPN)	Steinernema ceratophorum partitivirus 1 (ScPV-1)	*Partitiviridae*	RNA, bipartite, N/A	Double, N/A	1	N/A	N/A	[35]
B. malayi	Brugia malayi RNA virus 1 (BMRV1)	*Togaviridae*	RNA, N/A, positive	Single, approximately 7.8 kb	1	Diverse	Putative vertical or sexual	[21]
O. volvulus	Onchocerca volvulus RNA virus 1 (OVRV1)	*Rhabdoviridae*	RNA, N/A, negative	Single, N/A	1	Diverse	Vertical, horizontal	[21,36]
	Onchocerca volvulus RNA virus 2 (OVRV2)	Dicistroviridae	RNA, N/A, positive	Single, N/A	1	Diverse		[21,36]

NC, not categorized; N/A, not available. *: noda-like. PPNs, plant-parasitic nematode; SCN, soybean cyst nematode; PCN, potato cyst nematode; EPN, entomopathogenic nematode.

In addition to natural infection, experimental systems have been developed to ectopically express Orsay virus RNA1 and RNA2 as cDNAs under a heat shock promoter, enabling controlled expression of viral proteins directly in host cells independent of viral exposure and entry [47,48]. This approach expands the experimental versatility of the Orsay virus system, allowing precise dissection of antiviral defense mechanisms without the confounding effects of viral entry and transmission.

Complementing studies of Orsay virus infection, several groups have used *C. elegans* as a host for viruses that do not naturally infect this species. Early host-virus studies performed in *C. elegans* relied on infection of primary embryonic cell cultures with vesicular stomatitis virus (VSV), also known as Indiana vesiculovirus, an arbovirus from the *Rhabdoviridae* family that infects mammals [7,49,50,51]. Subsequent studies using VSV, including viral injection and ectopic expression of viral transcripts, helped establish the role of RNAi in antiviral defense and highlighted the importance of Dicer enzymes in small interfering RNAs (siRNAs) generation [7,49,52]. In parallel, a transgenic *C. elegans* strain was generated to express viral RNAs from Flock House virus (FHV) from the *Nodaviridae* family, which infects insects [53]. Although both VSV- and FHV-based systems support viral replication, and VSV can undergo vertical transmission, these models bypass key aspects of the natural viral life cycle, including physiological routes of entry, tissue tropism, spread within the host, and viral exit from infected cells [7,49,53]. As a result, these models are limited in their ability to capture the full dynamics of host–virus interactions *in vivo*, underscoring the importance of Orsay virus for studying antiviral defense mechanisms in *C. elegans.*

3. Antiviral Response of *C. elegans*

C. elegans lack the canonical Toll-like Receptor (TLR)/NF-κB pathway that mediates antiviral immunity in vertebrates, although it encodes a single TLR homolog, TOL-1, which functions in bacterial pathogen avoidance rather than in antiviral defense [54,55]. Consistent with this, Orsay virus enters *C. elegans* intestinal cells through an as-yet undefined receptor at the apical surface, establishing a productive but non-lethal infection [5,26]. Successful viral entry and infection depend on several host factors, including VIRO-2, SID-3, NCK-1, and DRL-1 (Fig. 2) [28,48,56]. VIRO-2 is an ortholog of the human Wiskott-Aldrich syndrome proteins (WASPs) and is likely required for successful Orsay virus infection as part of a kinase signaling pathway involving the nonreceptor tyrosine kinase SID-3 and tyrosine kinase adaptor protein NCK-1 [48,57,58]. In addition, the dietary restriction-like gene *drl-1* encodes a serine/threonine kinase required for Orsay virus entry but is dispensable for viral replication once the virus has entered intestinal cells [56].

Once Orsay virus successfully invades the host cell, the *C. elegans* anti-viral response relies on DRH-1, a DExD/H-box helicase and RIG-I-like receptor (RLR) homolog, which functions as a putative pattern recognition receptor (PRR) detecting viral double-stranded RNA (dsRNA) intermediates (Table 2, Ref. [7,8,21,25,27,29,30,49,53,59,60,61,62,63,64,65,66,67,68,69,70,71]) [9,47,59]. In mammals, RLRs are cytoplasmic sensors of viral RNA pathogen-associated molecular patterns (PAMPs) required in anti-viral immunity, and multiple RNA viruses in mammals interfere with RLR function to ameliorate the immune response [72,73,74]. Recognition of viral dsRNA by DRH-1 is essential for triggering two major antiviral immune responses in *C. elegans*—antiviral RNAi and the Intracellular Pathogen Response (IPR) (Table 2) (Fig. 2) [9,47]. The importance of DRH-1 in natural antiviral defense was first revealed through wild isolates: the strain from which Orsay virus was originally isolated carries a loss-of-function mutation in *drh-1* and is highly susceptible to infection, accumulating much higher viral loads than wild-type strains [5,6,75]. Consistently, laboratory-generated *drh-1* mutants also show dramatically enhanced viral replication, demonstrating that DRH-1–dependent antiviral mechanisms are central to resistance against Orsay virus in *C. elegans* [9,47,59,76]. Beyond Orsay virus, DRH-1 also restricts VSV to the site of injection, preventing viral spread and supporting its broader role in antiviral immunity.

Upon detection of viral dsRNA by DRH-1 and the dsRNA-binding protein RDE-4, viral RNA is processed by the Dicer enzyme into siRNAs [59]. These siRNAs are loaded onto the Argonaute protein RDE-1 to guide sequence-specific degradation of viral genomes [60,77]. Core RNAi factors, including RDE-1 and its partners, are essential for silencing, and *rde-1* mutant worms are frequently used experimentally to achieve higher viral loads, facilitating mechanistic studies [8,41,48,50,52]. Secondary siRNAs are amplified by RdRp polymerases, and act through secondary Argonautes to enable robust degradation of viral RNA and systemic antiviral protection (Fig. 2) [78]. In mammals, small RNA pathways can contribute to antiviral immunity: siRNAs, PIWI-interacting RNAs (piRNAs), and transfer RNA–derived fragments (tRFs) may directly target some viral nucleic acids in particular settings, whereas microRNAs (miRNAs) have a well-established role in regulating endogenous genes critical for innate immune responses [79,80,81,82,83]. Although mammals rely primarily on protein-based interferon signaling, these small RNA–mediated mechanisms reveal conserved principles of sequence-specific viral recognition, amplification, and silencing that parallel the antiviral strategies observed in *C. elegans* [61].

Whereas *C. elegans* lacks canonical interferon pathways, it has evolved the IPR, a transcriptional program that shares several regulatory and functional similarities with

Table 2. Overview of known antiviral mechanisms in soil-dwelling and parasitic nematodes.

Nematode species	Virus	Known antiviral mechanisms	Viral sensor	Transcription factors & chromatin remodelers	Lethality	Refs
C. elegans	Orsay virus	IPR	DRH-1	ZIP-1, MES-4, ISW-1, SynMuv factors	Non-lethal	[61,62,63,64,65,68,71]
		RNAi	DRH-1, RDE-4	N/A		[7,49,53,59,60,69]
		STA-1 pathway	N/A	STA-1		[66,67]
		3' uridylation	CDE-1	N/A		[8]
C. briggsae	Le Blanc virus	RNAi	N/A	N/A	Non-lethal	[25,27,29,30]
	Santeuil virus	RNAi IPR, partial				[25,29,30,70]
	Mělník virus	RNAi				[29]
B. malayi	BMRV1	RNAi	N/A	N/A	N/A	[21]

N/A, not available.

the type I interferon response in mammals [61,84]. Both pathways rely on RLRs to detect viral dsRNAs, with DRH-1 in *C. elegans* and RIG-I in mammals, initiating downstream signaling cascades that elicit protective transcriptional responses (Fig. 2) [47,85]. IPR activation provides resistance to Orsay virus but also confers protection against molecularly distinct fungal pathogens from the Microsporidia phylum [62,63,86,87,88]. The only obvious commonality between these pathogen classes is their obligate intracellular lifestyle, which inspired the naming of the IPR and distinguishes it from responses to extracellular bacterial pathogens in the intestine [62]. The IPR also contributes to protein homeostasis (proteostasis), facilitating the clearance of protein aggregates and modulating resistance to heat shock [62,63,89,90,91,92]. This parallels the mammalian type I interferon response, in which disruption of the proteasome induces interferon signaling and upregulation of immunoproteasome components [93]. Importantly, prolonged activation of both the IPR and the interferon response imposes developmental costs, manifesting as developmental delay and a shortened lifespan in *C. elegans*, and developmental abnormalities associated with inflammatory and autoimmune disorders in humans [62,94].

The IPR is characterized by the strong upregulation of 80 canonical IPR genes, with hundreds of additional genes induced at lower levels [62]. While mammalian interferon-stimulated genes (ISGs) encode many well-defined antiviral effectors, such as MX proteins, OAS, and PKR, IPR genes do not correspond to classical ISGs and most of them remain poorly characterized at the functional level [61,95]. Notable exceptions include components of the cullin-RING ubiquitin ligase complex, which participate in proteostasis [91,96,97]. Their role in antiviral defense is less well studied, although loss of the core component CUL-6 is associated with increased viral load (Fig. 2) [96]. Another key subset of IPR genes includes members of the protein containing ALS2CR12 signature (*pals*) gene family, which has expanded to 39 members (including one pseudogene) in *C. elegans* [62,98,99]. By comparison, mammals contain only a single *pals* homolog with unknown molecular function. The majority of, but not all, *pals* genes are induced as part of the IPR, yet none have an established antiviral function. For example, *pals-5*, one of the most strongly induced IPR genes and a common reporter for the pathway, contributes to proteostasis but not clearly to immunity [96]. Conversely, *pals-14* has recently been implicated in defense against microsporidia, although its role in viral immunity remains untested [87]. In addition, several *pals* genes that are not part of the IPR function as antagonistic regulators of this pathway [98,100]. Loss-of-function mutations in the IPR inhibitors *pals-17* and *pals-22*, and a gain-of-function mutation in the IPR activator *pals-25*, lead to constitutive IPR activation and confer enhanced resistance to Orsay virus infection (Table 2) [88,100,101].

In addition to *pals* genes, IPR regulation depends on transcriptional and chromatin factors, many of which belong to the Synthetic Multivulva (SynMuv) family [71,102,103]. SynMuv genes are largely conserved developmental regulators, and some repress IPR gene expression by acting through chromatin modifiers such as MES-4, a histone H3K36 methyltransferase, and ISW-1, an ATP-dependent chromatin remodeler (Table 2) [64,65,68,71,104,105,106,107]. Several SynMuv genes also encode components of the SUMOylation machinery, a posttranslational modification pathway that suppresses the IPR, at least in part by regulating DRH-1 function [11,71]. Metabolic signals further modulate the IPR: accumulation of deoxyadenosine due to mutations in specific enzymes in the purine salvage pathway triggers constitutive IPR activation, reminiscent of regulation of type I interferon in mammals [61,92,108].

All known regulatory pathways controlling the IPR require, at least in part, the bZIP transcription factor ZIP-1 (Table 2) [63]. Approximately one-third of IPR genes are regulated by ZIP-1, and loss of this factor increases susceptibility to Orsay virus, highlighting the antiviral function of ZIP-1–dependent genes (Fig. 2) [63]. The remaining ZIP-1–independent IPR genes appear to play a more

prominent role in defense against microsporidia, although the transcription factors regulating this subset remain unknown [63]. Given the expansion of the bZIP family in *C. elegans* and its established roles in antibacterial immunity in worms and plants, other bZIP transcription factors likely contribute to the regulation of these remaining IPR genes [63].

In mammals, Signal Transducers and Activators of Transcription (STAT) proteins are key transcription factors regulating interferon signaling, with STAT1 and STAT2 forming the interferon-stimulated gene factor 3 (ISGF3) complex, which activates antiviral gene expression, while STAT3 acts as a negative regulator [109,110]. *C. elegans* encodes two STAT homologs, STA-1 and STA-2 [66,111]. Whereas STA-2 has no demonstrated antiviral function, STA-1 acts as a repressor of antiviral gene expression in *C. elegans* [67]. STA-1 contains canonical STAT domains, including a DNA binding domain, an SH2 domain, and a putative tyrosine phosphorylation motif, enabling its function as a transcription factor (Table 2) [66].

Repression of *sta-1* leads to transcriptional changes that enhance resistance to Orsay virus, with limited overlap with the IPR [67]. Regulation of a subset of IPR genes by STA-1 further highlights regulatory parallels between the IPR and the type I interferon response (Fig. 2). However, the increased resistance observed upon loss of STA-1 is unlikely to be explained solely by partial IPR activation. This effect also appears to be independent of the RNAi pathway, as STA-1 functions separately from the RNAi factor RDE-3 [67]. Therefore, STA-1 may regulate a distinct antiviral program that remains to be defined. Interestingly, mutation of the kinase SID-3, which is associated with viral entry, reduces *sta-1* expression, suggesting that SID-3 may act upstream to phosphorylate STA-1 (Fig. 2) [67]. It is possible that Orsay virus entry disrupts the canonical SID-3 signaling, leading to reduced STA-1 phosphorylation and loss of its repression of antiviral genes [67]. Phosphorylation is a key regulatory mechanism for mammalian STAT proteins as well, where it controls their activation and antiviral gene expression, suggesting a shared regulatory principle across species [112].

An additional factor implicated in antiviral defense in *C. elegans* is the gene *cde-1* [8]. *cde-1* encodes a homolog for mammalian terminal uridylyltransferases TUT4 and TUT7, enzymes that catalyze the uridylation of RNA 3' ends, marking them for degradation [113]. Terminal uridylyltransferases target RNAs that lack poly(A) tails or contain short poly(A) tails [113]. Because Orsay virus RNAs lack poly(A) tails, their 3' ends might serve as PAMPs [8]. Consistent with this model, CDE-1 uridylates Orsay virus RNAs and promotes their degradation in an RNAi-independent manner, suggesting a conserved antiviral surveillance strategy shared with mammals (Table 2) (Fig. 2) [8].

Alongside the antiviral mechanisms described above, structural components of cells including actin filaments and IFs function as physical barriers to Orsay virus infection (Fig. 2). Disruption of actin networks comprising these structural barriers mediates antiviral immunity, likely by preventing Orsay virus entry into intestinal cells [114]. Conversely, the protein ACT-5 is an intestinal-specific actin shown to spatially associate with free Orsay virus δ proteins along the apical side of infected intestinal cells, and partial disruption of ACT-5 reduces Orsay virus egress [40]. Therefore, ACT-5 does not provide antiviral defense against Orsay virus, instead aiding in successful viral egress, highlighting the key roles structural components play in *C. elegans* immunity.

Together, the diverse antiviral mechanisms deployed by *C. elegans* against viral infection, including RNAi, the IPR, STA-1-dependent regulation, terminal uridylation, and structural defense, underscore the strong evolutionary pressure applied by viral infection (Fig. 2). Although Orsay virus remains the only virus known to naturally infect *C. elegans*, additional viral pathogens likely circulate within natural nematode populations. This potential viral diversity has possibly driven the evolution of multiple, complementary antiviral pathways, providing robust protection against a wide range of threats.

4. Viral Infection and Antiviral Response in *C. briggsae*

Building on insights from *C. elegans*, *C. briggsae* provides a complementary model to study viral infections and antiviral defense in nematodes [115]. Although the two species diverged roughly 100 million years ago, they share very similar morphology, behavior, and ecological niches [115,116]. Comparative genomics shows that approximately 62% of *C. briggsae* protein-coding sequences have orthologs in *C. elegans*, facilitating cross-species analyses of antiviral pathways [116].

To date, three closely related noda-like (nodavirus-like) viruses have been identified in wild *C. briggsae*: Santeuil virus and Le Blanc virus, both isolated in France, and Mělník virus, discovered in Czechia (Fig. 1) [5,27,29]. Similar to Orsay virus in *C. elegans*, these viruses are bipartite, positive-sense single-strand RNA viruses, with RNA1 encoding an RdRp and RNA2 encoding the capsid and δ proteins [5,27,29,117].

All three *C. briggsae*-infecting viruses rely on horizontal transfer via the fecal-oral route, with excreted virions passing through the intestine for consumption and infection of nearby nematodes [25]. They share intestinal tropism with Orsay virus in *C. elegans*, infecting intestinal cells and causing cellular damage [25,29,30]. Despite many similarities between *C. briggsae* and *C. elegans*, naturally occurring viruses in these species exhibit strict host specificity. *C. briggsae* shows no sensitivity to Orsay virus, whereas *C. elegans* is resistant to the three noda-like viruses that in-

fect *C. briggsae* [25,29,30]. Even *C. elegans drh-1* mutants, which display increased susceptibility to Orsay virus, cannot be infected by Santeuil virus and Le Blanc virus, highlighting a strong species barrier to infection [5,27].

Susceptibility also varies among *C. briggsae* isolates. For example, several strains isolated from tropical regions are resistant to viral infection, whereas isolates from the temperate climates show susceptibility [30]. In addition, some *C. briggsae* strains are susceptible to Santeuil virus but resistant to Le Blanc virus, indicating virus-specific differences in host compatibility [30]. In susceptible populations, however, noda-like viruses can co-infect not only the same animal but even the same intestinal cell, demonstrating shared tissue tropism and overlapping infection niches [29].

Variation in susceptibility among nematode strains suggests differences in antiviral defense mechanisms. Like Orsay virus infection in *C. elegans*, susceptible *C. briggsae* strains mount a detectable antiviral response to noda-like infection (Table 2) [30]. Notably, resistance in *C. briggsae* does not appear to result from enhanced RNAi activity [30]. In resistant strains, viral small RNAs are largely absent despite an intact RNAi machinery, suggesting that resistance may instead arise from defects in viral entry or very early steps of the viral life cycle [30].

Santeuil virus infection also induces a robust transcriptional response in *C. briggsae* [70]. Transcriptomic analyses identified 57 orthologous genes that are upregulated during Orsay virus infection in *C. elegans* and Santeuil virus infection in *C. briggsae* [70]. Several of these genes overlap with components of the IPR in *C. elegans*, including members of the *pals* and C-type lectin (*clec*) families (Table 2) [70,100,118]. Notably, the *pals* gene family is much less expanded in *C. briggsae* than in *C. elegans*, comprising only eight members [98,101]. In contrast, orthologs of several other IPR genes, such as those encoding cullins or the exonuclease EOL-1, are not induced upon Santeuil virus infection [70,118]. Together, these findings suggest that viral infection in *C. briggsae* triggers a transcriptional response that partially overlaps with the IPR but is not identical to it. Further studies are needed to determine the functional contribution of this response to antiviral defense and whether it varies across different viral infections.

5. Viral Infections and Anti-Viral Defenses of Plant-Parasitic Nematodes

Insights gained from free-living nematodes such as *C. elegans* and *C. briggsae* provide a solid foundation for understanding antiviral immunity in nematodes. However, nematodes also include a large and diverse group of parasitic species that exert substantial ecological, agricultural, and public health impacts [20,119,120]. Examining viral infections in these organisms expands the relevance of nematode antiviral studies beyond laboratory models and into natural and economically important systems.

Parasitic nematodes infect a wide range of plant and animal hosts and are responsible for major health and economic burdens worldwide. In this section we will focus on plant parasitic nematodes, responsible for extensive agricultural losses each year [14,120,121]. Despite their high prevalence and impact, viral pathogens of parasitic nematodes have historically received little attention, in part due to the previously prevailing belief that PPNs are largely immune to viral infection [122].

Contrary to this belief, the first virus known to infect a nematode was reported in 1959 in the southern root-knot nematode *Meloidogyne incognita* [123]. However, it was not until the breakthrough of next-generation sequencing technologies in the 2000's that viruses associated with PPNs began to be identified more broadly [31,32]. Viral infections of agriculturally important species, such as the soybean cyst nematodes (SCN), which reduces soybean yields by approximately 10–30% annually, are now increasingly recognized as a critical area of study [12,31,124].

High-throughput sequencing and genome assembly of the SCN *Heterodera glycines* revealed four negative-sense single-stranded RNA viruses present across multiple life stages, including eggs and juveniles [31]. The presence of viral sequences in early developmental stages suggests vertical transmission from adults to progeny, in contrast to the lack of vertical transmission observed in naturally occurring viruses of *C. elegans* and *C. briggsae* [5,31]. These viruses include socyvirus-1 (soybean cyst nematode virus 1; SbCNV-1, also known as ScNV), phlebovirus (ScPV), and rhabdovirus (ScRV), which belong to the families *Nyamiviridae*, *Bunyaviridae*, and *Rhabdoviridae*, respectively, as well as tenuivirus (ScTV), which currently lacks formal family classification. A subsequent study identified an additional positive-sense single-stranded RNA virus, soybean cyst nematode virus 5 (SbCNV-5), a pestivirus in the family *Flaviviridae*, in *H. glycines* across multiple life stages, with evidence suggesting potential sexual transmission by males (Table 1) [32]. Interestingly, some of these viral families include important human pathogens such as Rift Valley fever virus, rabies virus, and Zika virus [125,126,127].

In addition to sequencing-based discovery, independent analyses of field populations confirmed active infection and replication of all five identified viruses in *H. glycines*, with qRT-PCR detection of both genomic and antigenomic viral RNA across egg and juvenile stages [128]. Using the same approach, viruses were also detected in related cyst nematode species, with ScPV, SbCNV-1, and ScTV identified in the clover cyst nematode *Heterodera trifolii*, and ScPV and ScRV in the beet cyst nematode *Heterodera schachtii*. These results suggest greater host range flexibility among PPN viruses compared to those infecting free-living nematodes [128].

A subsequent study in an inbred population of SCN identified two additional negative-sense RNA viruses

named nyami-like virus (NLV) and bunya-like virus (BLV) (Table 1) [33]. Viral infection throughout pre-parasitic second-stage juveniles was visualized *in situ* using FISH with RNA transcripts of SbCNV-1, NLV, and BLV [129]. Consistent with these observations, viral transcripts were also detected in eggs and genital primordia, further supporting vertical transmission. Importantly, SCN RNA viral transcripts were not observed in intestinal cells, distinguishing these viruses from the strict intestinal tropism of horizontally transmitted RNA viruses in *Caenorhabditis* species. Furthermore, a positive-sense RNA virus, the picorna-like virus (PLV), was identified in the potato cyst nematode (PCN) *Globodera pallida* (Table 1) [33].

Together, these studies demonstrate that PPNs host a diverse viral community, underscoring the complexity of their biology as these organisms need to defend against both viral infection and plant immune responses. This diversity also raises important questions about whether viral infection alters nematode pathogenicity or modulates plant-nematode interactions.

In contrast to free-living nematodes, where multiple levels of antiviral defense have been defined, little is known about immune mechanisms in PPNs. Given the strong conservation of the RNAi pathway, it is reasonable to propose that antiviral RNAi may contribute to immune defense in PPNs. Indeed, a recent study reported robust production of virus-derived siRNAs against three viruses in the potato cyst nematode *Globodera rostochiensis* and three viruses in the beet cyst nematode *H. schachtii*, suggesting that antiviral RNAi is functional in PPNs [130]. Interestingly, two Nyami-like viruses elicited only weak siRNA responses, suggesting possible evasion of RNAi or the involvement of additional antiviral mechanisms [33]. However, studying antiviral immunity in these organisms presents technical challenges because PPNs have a distinct life cycle and do not feed during their soil-dwelling, pre-parasitic stages [131]. Additionally, the isolation and propagation of PPN-infecting viruses remain limited, constraining direct analysis of antiviral responses compared to free-living nematode models.

Despite these challenges, several experimental approaches have demonstrated that RNAi is functional in PPNs. Early studies showed that RNA uptake could be induced in the infective second-stage juveniles of *H. glycines* and *G. pallida* by stimulation with octopamine, enabling the knockdown of cysteine proteinases that alter plant growth upon infection [132]. A complementary strategy involved *in planta* delivery of dsRNAs, in which transgenic host plants were engineered to express dsRNAs targeting specific nematode genes [133,134]. Silencing of genes associated with parasitism through these methods resulted in impaired nematode development and reduced infection success, demonstrating that RNAi-mediated post-transcriptional gene regulation is conserved and functional in PPNs [133,134,135]. These findings suggest that RNAi may represent an important antiviral defense mechanism in PPNs; however, its direct role in antiviral immunity remains to be established. Given the variable relevance of RNAi as an antiviral mechanism in different contexts, additional or alternative antiviral defenses are likely to play a role in PPN immunity. For example, it is possible that PPNs mount antiviral transcriptional responses analogous to the IPR in *C. elegans*. Future studies defining viral infection dynamics and host responses in PPNs, together with improved genetic tools, will be important for understanding antiviral defense in these species.

6. Viral Infection and Antiviral Responses of Animal-Parasitic Nematodes

In addition to PPNs, nematodes are also important parasites of animals, including humans, causing widespread disease [13,136]. For example, the most common parasitic infections in humans are ascariasis and hookworm, with approximately one billion individuals infected with *Ascaris lumbricoides* and 470 million infected with hookworm worldwide [13,137,138,139]. Furthermore, insect-transmitted filarial nematodes, including *Wuchereria bancrofti*, *Brugia malayi*, and *Onchocerca volvulus*, cause regionally restricted outbreaks of lymphatic filariasis [140,141].

Recently described viruses infecting animal-parasitic nematodes (APN) have substantially expanded our understanding of host-virus interactions in pathogenic nematodes [21]. By mining publicly available transcriptomic datasets, a recent study identified a broad diversity of RNA viruses associated with parasitic nematodes, including members of the families *Totiviridae*, *Partitiviridae*, *Rhabdoviridae*, and *Lispiviridae* [21]. Notably, *Rhabdoviridae* include viruses infecting both filarial nematodes and PPNs, suggesting deep evolutionary association between specific viral families and nematodes (Table 1) [21,31].

These findings build on earlier reports showing that viruses are not restricted to filarial species but also occur in other APNs, including entomopathogenic nematodes (EPNs). For example, a partitivirus was identified in the EPN *Steinernema ceratophorum*, representing the first virus described from this group [35]. This virus has a simple bipartite dsRNA genome encoding an RdRp and a coat protein, consistent with members of the family *Partitiviridae* (Table 1) [35]. However, the antiviral response of *S. ceratophorum* has not yet been characterized, making it an important area for future research to determine whether its immune mechanisms are conserved or represent distinct strategies compared to those in *C. elegans*.

Within APNs, currently the best understanding of viral infections comes from the filarial species *B. malayi* and *O. volvulus*. *B. malayi* is spread by mosquitoes, including *Aedes aegypti*, and establishes chronic infections in the lymphatic system, leading to lymphedema and, rarely, elephantiasis [142,143]. Transcriptomic analyses revealed

the presence of Brugia malayi RNA Virus 1 (BMRV1), a positive-sense, single-stranded RNA virus from the *Togaviridae* family [21]. The viral genome is 7.8 kb and encodes a large polyprotein that includes an RdRp with additional methyltransferase and helicase domains, as well as a small capsid protein [21]. Viral transcripts of BMRV1 were detected across multiple life stages examined in a laboratory strain of *B. malayi*, with the largest proportion of viral transcripts detected in adults (Table 1) [21]. In contrast to the intestinal localization of RNA viruses in *Caenorhabditis* spp., or the broader cellular distribution observed in infected *H. glycines*, FISH staining of BMRV1 in adult *B. malayi* was restricted to tissues beneath the cuticle and the reproductive tract. This localization suggests potential vertical or sexual transmission.

Importantly, the presence of BMRV1 was associated with the production of siRNAs, suggesting a functional RNAi response as a part of anti-viral defense in *B. malayi*, similar to *C. elegans* response to Orsay virus infection (Table 2) [21,49]. The detection of secondary virus-derived siRNAs further suggests active viral replication and engagement of RdRp-driven amplification pathways [21]. Thus, the antiviral small RNA pathway is an important mechanism of anti-viral defense across multiple species of both parasitic and non-parasitic nematodes, illustrating the significance of evolutionary conserved mechanisms of defense.

Viral pathogens have also been identified in another filarial nematode *O. volvulus*, the causative agent of onchocerciasis, a leading cause of infectious blindness [144]. *O. volvulus* is transmitted by black flies (*Simulium damnosum*) and causes chronic dermatitis and ocular disease as the nematode migrates through host tissues [36,144]. Six viral transcripts in *O. volvulus* were discovered with the two full-length viral genome sequences named Onchocerca volvulus RNA Viruses 1 and 2 (OVRV1 and OVRV2) (Table 1) [21]. Notably, OVRV1 was detected in both *O. volvulus* and the closely related species *Onchocerca ochengi*, again contrasting with the strong host specificity observed for RNA viruses infecting *Caenorhabditis* species [21,25,29]. Although the antiviral response of *O. volvulus* has not yet been characterized, both BMRV1 and OVRV1 were found to elicit a seropositive response in vertebrate hosts infected with the parasites, implying that the APN-associated viruses may directly interface with the vertebrate immune system [21]. Among additional human parasitic nematodes screened for viral infection, the parasites *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma ceylanicum*, and *Trichinella spiralis* carried viral infections [21]. Taken together, these observations highlight parasitic nematodes as previously underappreciated hosts for diverse RNA viruses and raise important questions about how viral infection influences nematode biology, host–parasite interactions, and disease progression in vertebrate hosts. Further investigation of viral infection and antiviral responses in parasitic nematodes may reveal conserved or distinct mechanisms, providing a broader evolutionary context for antiviral defense pathways defined in *C. elegans* and *C. briggsae*.

7. Nematodes as Viral Vectors

Given their ecological abundance, mobility, and intimate interactions with hosts, nematodes are well positioned to act as vectors for viral transmission across diverse environments. Nematodes encounter viruses during feeding, migration, and host invasion, creating opportunities for virus persistence and dispersal. Consistent with this, nematodes have been implicated in transmission of bacteriophages through soil and compost, as well as economically important plant viruses [21,122,145,146,147]. For example, nematodes *Xiphinema rivesi*, *Xiphinema americanum*, and *Longidorus attenuatus* are vectors for tobacco ringspot virus, tomato ringspot virus, and tomato black ring virus, respectively [148,149,150,151]. Unlike arthropod vectors, these nematodes typically do not support viral replication. Instead, viral particles are acquired during feeding on infected plants and persist through stable attachment to specific anatomical structures [147]. For example, viral particles associate with the mouthparts of *Longidorus* species, whereas in *Xiphinema* species they bind to the esophageal lining [148,152]. Mechanistically, these interactions possibly involve capsid–ligand interactions that allow viral particles to persist on nematode surfaces without compromising feeding or development [153,154,155]. Supporting this model, viral attachment in *Xiphinema diversicaudatum* depends on a carbohydrate layer lining the esophagus and odontophore [147,156]. Remarkably, these viruses can remain infectious within nematode vectors for extended periods, often until the next molt, enabling long-term transmission across spatially separated hosts [147,157,158]. Transmission is thought to occur during feeding on a new host plant, mediated by mechanical damage and glandular secretions released during parasitism, representing an efficient “piggybacking” strategy that preserves nematode fitness [122,152,153,158,159].

The association of plant viruses with PPNs exhibits clear specificity, consistent with co-evolution between viruses and vectors. For example, grapevine fanleaf virus is acquired by the nematode *Xiphinema index* from both grapevine and quinoa plants but is transmitted only to grapevine [158,160,161]. Taken together, these observations highlight a close evolutionary relationship between plant viruses and their nematode vectors, in which precise physical interactions govern host range and transmission efficiency.

Beyond passive carriage, emerging evidence suggests that viruses may actively shape nematode–plant interactions to enhance transmission. Infection of the tobacco plant *Nicotiana benthamiana* with tobacco rattle virus alters plant volatile profiles, increasing the production of compounds that attract trichodorid nematodes and promote

feeding [22]. Such virus-induced manipulation of host signaling highlights a tri-partite interaction in which viral infection modifies plant behavior to recruit nematode vectors, thereby facilitating viral spread.

Emerging evidence suggests that viruses associated with APNs could modulate host immune responses and potentially contribute to pathogenesis. For instance, viral infection of *O. volvulus* is proposed to play a role in the development of onchocerciasis-associated epilepsy [162]. Phylogenetic analyses further indicate that several viruses found in filarial nematodes are related to known human pathogens, raising the possibility that these nematodes may act more as vectors than true hosts, facilitating the transfer of viral factors that affect host physiology [21].

In summary, these studies establish parasitic nematodes as effective and evolutionarily refined viral vectors, particularly in plant systems, while emerging data from APNs suggests broader relevance across ecological contexts. Understanding how nematodes balance viral carriage, host interactions, and their own immune defenses will be critical for disentangling the evolutionary and mechanistic principles governing virus transmission in both agricultural and medical settings.

8. Conclusions and Future Perspectives

Over the past decade, nematodes have emerged as a valuable system for studying viral infection, antiviral defense, and virus–host interactions across diverse ecological contexts. Research in free-living nematodes, particularly *C. elegans*, has provided detailed insights into antiviral immunity at whole-organism resolution, revealing how small RNA pathways, transcriptional immune programs, and post-transcriptional RNA regulatory mechanisms cooperate to limit viral replication. These findings demonstrate that effective antiviral defense is achievable in the absence of canonical interferon signaling, while still relying on evolutionarily conserved principles such as viral RNA recognition, signal amplification, and coordinated transcriptional responses.

Importantly, the IPR shares several key conceptual and mechanistic similarities with the mammalian type I interferon response [61]. Both responses are initiated by RIG-I-like receptors that sense viral double-stranded RNA and induce broad transcriptional programs that promote pathogen resistance and cellular homeostasis [47,61,76]. Although the molecular components differ, the parallels between the IPR and interferon signaling underscore the value of free-living nematodes as simplified systems for dissecting conserved principles of antiviral immunity, including how immune activation is regulated and integrated with cellular physiology.

Despite these advances, our understanding of viral diversity in free-living nematodes remains remarkably limited. To date, only four viruses are known to naturally infect free-living nematodes, with all isolated from a narrow geographic range in Western and Central Europe (Fig. 1) [5,25,29]. This restricted sampling strongly suggests that myriad additional viruses remain undiscovered in natural nematode populations worldwide. Expanding viral discovery efforts across broader ecological and geographic scales represents a major opportunity to uncover new modes of infection, host specificity, and immune adaptation, and will further strengthen the utility of nematodes as models for antiviral research.

Beyond free-living species, accumulating evidence demonstrates that parasitic nematodes harbor a diverse array of viruses. In PPNs, viral interactions are best understood through their dual roles as hosts of nematode-infecting viruses and as vectors of plant viruses [145,153,163]. However, this vectorial role is not restricted to passive carriage: viral infection of plants can actively reshape plant–nematode interactions [22]. Consequently, plant viruses function as dynamic components of plant–nematode–virus systems rather than acting solely as cargo during transmission. The rapid discovery of viral infections in myriad PPNs also illustrates their potential as alternative models for antiviral immunity and infection. Future work should define the prevalence and mechanisms of antiviral RNAi in PPNs, determine whether transcriptional responses analogous to the IPR operate in these species, and assess how these defenses influence viral infection, nematode fitness, and plant–nematode interactions.

In APNs, recent transcriptomic surveys have revealed widespread and persistent viral infections, particularly in filarial species [21]. The detection of virus-derived siRNAs in *B. malayi* provides evidence consistent with antiviral RNAi activity, suggesting partial conservation of antiviral defense strategies described in *Caenorhabditis* species [7,21,76]. At the same time, the absence of functional data for most species highlights how little is currently known about antiviral immunity in parasitic nematodes and underscores the need for mechanistic studies beyond sequence-based discovery. Additionally, APNs that infect humans are difficult to obtain and maintain in a laboratory setting, especially given the geographical and geopolitical restrictions of transporting filarial disease-causing parasites like *O. volvulus* [36,144,164]. Addressing these limitations will require the development of tractable experimental systems, including improved methods for parasite maintenance, viral isolation, and genetic manipulation, to enable direct investigation of antiviral mechanisms in parasitic nematodes.

An emerging and particularly intriguing theme is the interface between parasitic nematode-associated viruses and host organisms. The observation that filarial viruses elicit serological responses in infected vertebrates raises important questions about how viral products contribute to host immune activation and disease processes. While causal links between nematode-associated viruses and pathology remain unresolved, these findings expand the conceptual framework of nematode–host interactions and

motivate future studies that explicitly address virus-mediated effects on host physiology.

Despite substantial progress, much remains unknown about viral diversity, antiviral immunity, and transmission strategies in nematodes. Expanding viral discovery in free-living nematodes will be critical for understanding the evolutionary pressures that have shaped their diverse antiviral defenses. In parasitic nematodes, developing experimental tools to probe antiviral responses, viral persistence, and transmission mechanisms will be essential for linking viral infection to nematode fitness and host outcomes. This is especially important given the profound agricultural and health impact of parasitic nematodes, where viral infection may play pivotal roles in the evolution of both nematode and host immunity. More broadly, nematodes offer a rare opportunity to study antiviral immunity across free-living, plant-parasitic, and animal-parasitic lifestyles within a single phylum, emerging as invaluable alternative model systems to mammalian studies for understanding the dynamics of interferon-independent antiviral defense mechanisms.

Author Contributions

VL conceived the topic of review and overall structure. DH and VL conducted literature search and analysis. DH drafted the manuscript. VL and DH critically revised the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final version. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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