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Unlocking the secrets of *Feline calicivirus*: advances in structural and nonstructural proteins and its role as a key model for other *Caliciviruses*

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Abstract

Feline calicivirus (FCV) is a highly contagious pathogen responsible for respiratory infections, lingual ulceration, oral ulcers and systemic diseases in cats, posing a significant risk to feline family worldwide. Virus enters via nasal oral and conjunctival routes. Oropharynx is primary site of replication, induces epithelial necrosis. After recovery from acute disease most cats clear virus within 30 days. Some lifelong carriers via colonization of tonsillar and other tissues. Understanding the structural and nonstructural proteins of FCV is essential to know viral replication process, its pathogenesis and interaction with host immune system. This manuscript outlines the recent progress made on the characterization of FCV proteins with respect to their involvement in viral assembly, entry, immune evasion, and replication. Although structural proteins such as capsid have received most attention regarding viral attachment and host specificity, but nonstructural proteins are emerging as key players in influencing host cell activities and viral RNA synthesis. This review highlights the requirement for advanced structural research methods, large-scale antiviral screening, and thorough investigations into FCV-host interactions. These studies will not only enable us fully understand FCV, but also promote the progress of more universally applicable virological research and drug development.

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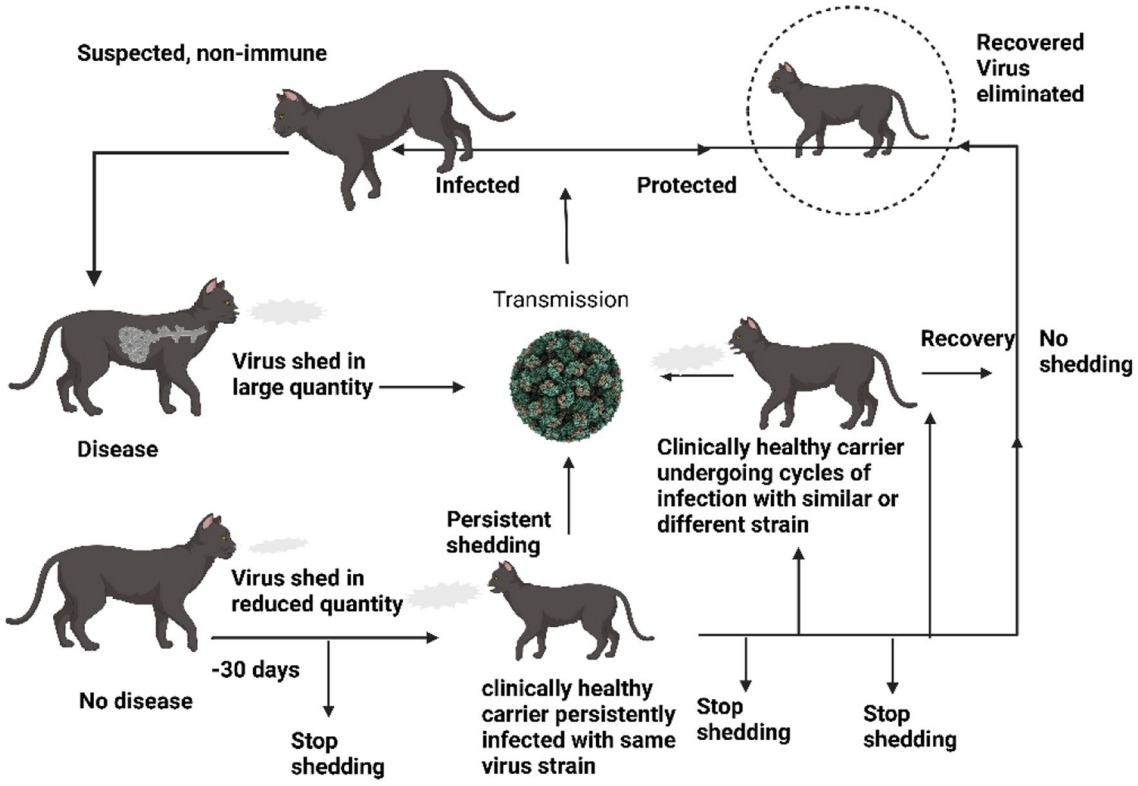
Graphical abstract



Keywords *Feline calicivirus* (FCV), Structural protein, Nonstructural protein, Vaccine development, Host-virus interaction

Introduction

Feline calicivirus (FCV) is a highly mutagenic RNA virus prevalent in domestic cats [1]. It belongs exclusively to the Felidae family and does not exhibit any zoonotic potential. There is significant heterogeneity in the genetic and antigenic composition of FCV [2]. Upper respiratory tract disease (URTD), lingual ulcerations, gingivostomatitis, limping syndrome, and in severe cases, virulent systemic FCV (VS-FCV) infection can cause alopecia, skin ulceration, oral cavity ulceration, pinnae, nares, and necrotising pododermatitis with serocellular crusts. Feline infections may result in many symptoms, such as subcutaneous oedema, bronchointerstitial pneumonia, and necrosis of the pancreas, liver, and spleen, all of which elevate mortality rates [3].

Calicivirus particles exhibit hexagonal or star-like configurations, featuring cup-shaped indentations in electron microscopic images; the term derives from the Greek word 'calyx,' signifying cup or goblet. This virus possesses a brief (7.5 kb) single-stranded RNA genome that is positively polarised (messenger), facilitating rapid evolution. Some members of this family are known to cause diseases in humans, including noroviruses; others are exclusive to animals, like *rabbit hemorrhagic disease virus* (RHDV) and *European brown hare syndrome virus* (EBHSV) [4]. Since viruses do not employ a proofreading system during reproduction, they are able to undergo rapid mutations and expand their evolutionary potential [5]. There are three operational open reading frames (ORFs) in the viral genome, which is non-segmented. VP1 protein represents the major component of virion capsid structure alongside protein VP2 which gets encoded from ORF3. In the final stages of infection, subgenomic RNA is converted into the structural proteins that genomic RNA encodes. An ORF2-encoded polyprotein is cleaved to provide two smaller proteins: the major capsid protein (VP1) and capsid leader (LC). In feline kidney cell cultures, *vesiviruses* can cause cell death, and the LC protein plays a key role in this process [6, 7].

Calicivirus belongs to a large family of viruses, although only a few members have the ability to replicate in cell culture (Table 1). One of the well-studied example is FCV which primarily infects domestic cats [8]. FCV often used as a model to understand *calicivirus* biology and develop

Table 1 Foundation of viral replication: cell lines and receptors

Genus	Type species	Host species	Receptors	Cell lines for viral replication	References
Bavovirus	*Bayern virus (avian)*	Chicken	Unknown	Primary chicken embryo fibroblast cells: low yield PCC cells and embryonal liver and fibroblast cells: Unsuccessful	[63, 64]
Lagovirus	*Rabbit hemorrhagic disease virus (RHDV)* *European brown hare syndrome virus (EBHSV)*	Rabbit	H type 2 HBGA	RK-13 cells	[65, 66]
Minovirus	*Fathead minnow calicivirus* (minnow)	Fishes	Unknown	EPC, FHM, CHSE-214, BF-2, or RTG-2 cell line	[67, 68]
Nacovirus	*Novel avian calicivirus* (chicken, turkey)	Turkey	Unknown	PCC cells : Unsuccessful	[64]
Nebovirus	*Newbury-1 virus* (NBV)	Bovine	BNeV: HBGAs and/or SAs	Bovine cells lines, e.g., MDBK and PEB: Unsuccessful	[69, 70]
Salovirus	*Atlantic salmon calicivirus* (salmon)	Salmon		GF-1 cell line	[71]
Sapovirus	*Sapporo virus* (SaV)	Humans, Pigs, Mink, Dogs, Sea lions, and Bats	porcine SaV (PSaV) : terminal SAs receptor	Porcine SaV: LLC-PK cells, human SaVs: Unsuccessful	[72–74]
Valovirus	*St Valérian virus (porcine)*	Swine	Unknown	Porcine kidney cell line (PK15) and a monkey cell line (MK2): Unsuccessful	[75]
Norovirus	*Norwalk virus (NV)*	Mammalian species, bats, sea lions, harbor porpoise, Humans and Murine species	human NoVs (HuNoVs), bovine NoV, canine NoVs : HBGAs, murine NoV (MNV): terminal SAs receptor, human NoVs: SAs	**HuNoV**: B cell line (BJAB), HIE cells, h-iPSC–derived IECs **MNV-1**: BV-2 cell line, RAW and TIB cells	[76–82]
Recovirus	*Tulane virus (simian)*	Monkeys	HBGAs, SAs	Monkey kidney cells LLC-MK2, Vero E6 cells	[83–85]
Vesivirus	*Vesicular exanthema of swine virus (VESV)* *Feline calicivirus (FCV)* *San Miguel sea lion virus (SMSV)*	Swine, Feline	FCV: junctional adhesion molecule-1 (JAM-1)	Crandell–Reese feline kidney (CRFK) cells	[86]

antiviral treatments due to its adaptability in laboratory settings. Virus entry into host cells is contingent upon the VP1 capsid protein, which comprises the N-terminal arm (NTA) structure, shell (S), and protrusion domain (P) components, subdivided into subdomains P1 and P2. The antigenic features of VP1 protein span from A to F yet the key region for feline junctional adhesion molecule-A (fJAM-A) receptor binding exists in E. fJAM-A exists as a compound of cellular tight junctions while its breakdown connects to oral and cutaneous ulcer formation. The recent study has shown that FCV uses clathrin-mediated endocytosis for cell entry alongside the requirement of endosomal acidification to completely uncoat viral DNA [9].

The FCV uncoating process depends on VP2 capsid protein which facilitates viral DNA exit into host cells [10]. VP1-VP2 interaction plays an important role in maintaining viral structural integrity along with functional aspects since researchers identified distinct linear neutralizing and non-neutralizing antibody epitopes present in VP1 [6]. Antigenic differences among FCV strains provide obstacles for attaining vaccination cross-protection. Nonetheless, the extent of similarity among strains allows for a degree of cross-protection [11].

Structural organization of FCV

Structural organization (Figs. 1A and 2B and C) refers to the way the virus is composed and how its components are arranged. The virus is surrounded by a protective protein coat called capsid. The capsid is made up of 60 copies of a major protein called VP1 (viral protein 1) which forms a T = 3 icosahedral symmetry. VP1 contain several antigenic sites, making it the target for immune response, while VP2 is a minor protein, which helps in stabilizing the structure. The positive sense RNA viral genome, organized with untranslated region (UTRs) at both ends and a coding sequence in between. This RNA genome upon entry into host cell, enables direct protein synthesis and acts as messenger RNA (mRNA) [12]. Unlike enveloped viruses, FCV is more resistant to environmental factors such as drying and detergents because it lacks lipid envelope. The virus enters host cells by binding to specific receptors, such as integrins or heparin sulfate like molecules, and internalized via endocytosis. Upon

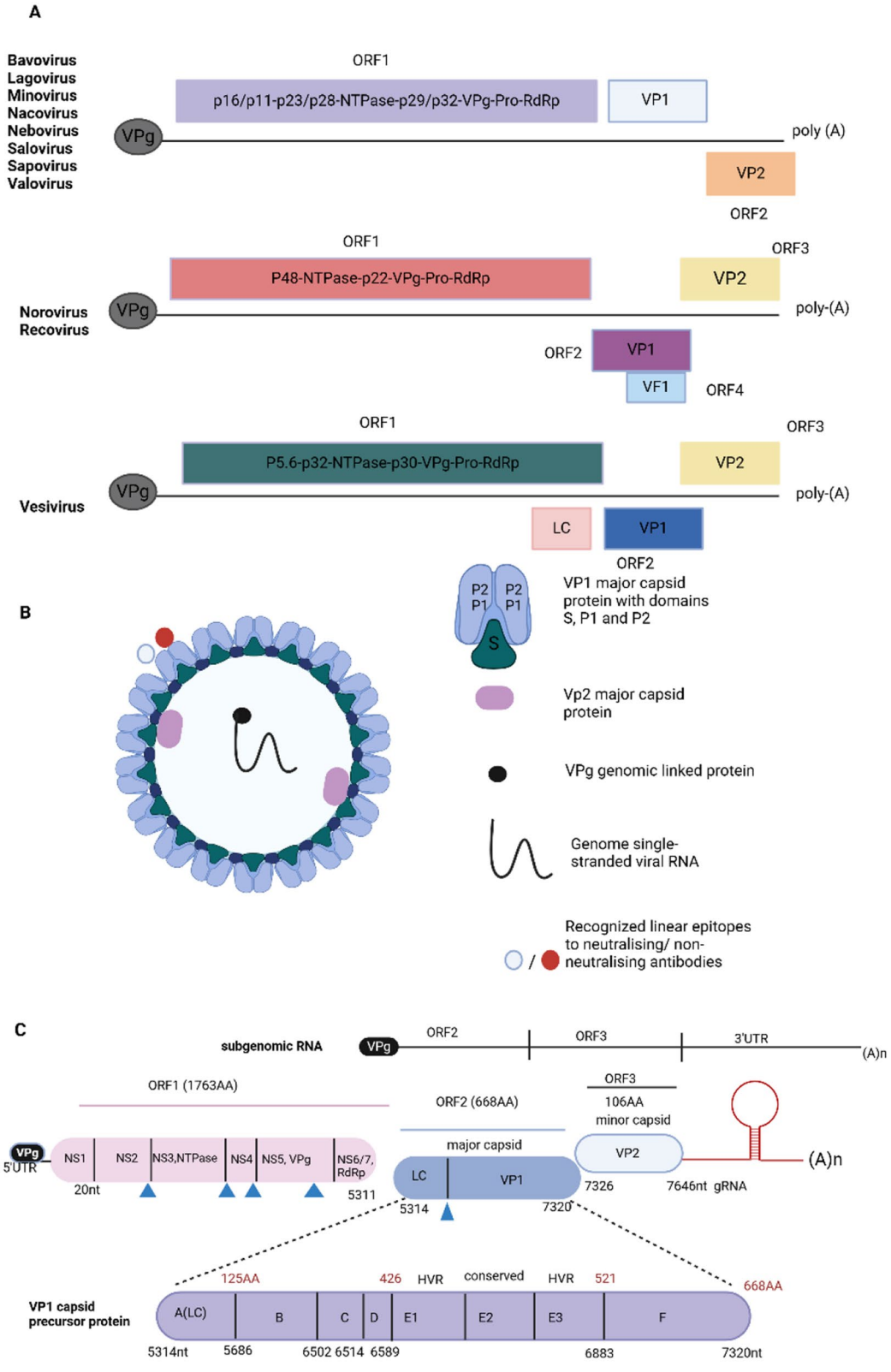


Fig. 1 (See legend on next page.)

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Fig. 1 **(A)** Phylogenetic relationships in the family *Caliciviridae* **(B)** FCV viral structure is depicted schematically. Both the capsid region F and a conserved section of E5′HVR were shown to have linear, non-neutralizing epitopes. Additionally, E5′HVR was found to contain linear, neutralizing epitopes, as shown by the red circles in the figure. VPg stands for virus protein. The NTR stands for the non-translated region. The abbreviation "NTPas" stands for nucleoside-triphosphatase. LC stands for capsid leader. HVR stands for hypervariable region. **(C)** Analysis of the genomic structure of FCV. Open reading frames (ORFs) 1–3, subgenomic RNA, antigenic regions (A–F) of the VP1 capsid precursor protein, and the structural domains of the VP1 protein are all included in the illustration. Whereas red numbers show the locations of amino acids in ORF2, black numerals indicate the locations of nucleotides in the viral genome. The blue triangle represents the NS6/7 cleavage sites. The terms LC, HVR, RdRp, gRNA, NTA, and S domain denote the capsid protein leader, the N-terminal arm, the hypervariable region, and the shell domain, respectively

entry, virus uncoats, allowing its genome to replicate and translate within the cytoplasm, often using intracellular membranes like the rough endoplasmic reticulum. Through lysis, newly assembled virions are released from the host cell, which facilitates viral spread but damages the infected cell. FCV is highly variable, particularly in its capsid region, enabling it to evade immune response and in some cases establish persistent infections [13]. This structural organization underpins the ability of FCV to infect, replicate and adapt in feline host.

Receptors for FCV entry into cells

The variations in viral interactions with their receptors influence tissue tropism, disease severity, and the host range of viruses [14]. Consequently, comprehending the specifics of FCV-receptor interactions will yield insights into these mechanisms. JAM-A is a type I transmembrane glycoprotein including two extracellular immunoglobulin (Ig)-like domains, D1 and D2, a transmembrane domain, and a brief cytoplasmic tail [15]. It is located in the tight junctions of endothelial and epithelial cells, where it governs the integrity and permeability of these junctions. It is also present on the surfaces of platelets, leukocytes, and erythrocytes, playing a role in leukocyte diapedesis and platelet aggregation [16]. The functional cell surface receptor for FCV is fJAM-A, and the insertion of fJAM-A into non-permissive Chinese Hamster Ovary (CHO) K1 cells renders them susceptible to FCV [14, 17] Given that viral attachment and entry are crucial stages in the pathophysiology of infection, comprehending the precise interactions between FCV and the fJAM-A ectodomain may be essential for clarifying VS-FCV infections. The knowledge of receptors involved in viral replication is important for advancing research in virology and developing targeted therapeutic strategies (Table 1).

Immunoglobulin superfamily member JAM-1 is expressed in various organs and cell types, including endothelial cells, epithelial cells, platelets, and leukocytes; it is specifically localised in apical tight junctions [18]. FCV predominantly infects the respiratory tract, except for strains causing severe systemic illness, suggesting that JAM-1 is a vital determinant of FCV host specificity and that other tissue-specific molecular components may play a role in localised FCV infection in vivo. When fJAM-1 molecules are transduced into cells that are not allowed to connect to FCV, they become vulnerable to infection [19]. In accordance with this idea, Crandell-Rees Feline Kidney (CRFK) cells subjected to neuraminidase therapy, subsequently followed by O-glycanase treatment, exhibited diminished FCV-binding capacity. Anti-fJAM-1 antibodies selectively prevent the virus from attaching to (CRFK) cells, which stops the virus from replicating inside the cells. The results demonstrate that fJAM-1 functions as a receptor for FCV. Consequently, carbohydrates present in particular tissues or cells may facilitate JAM-1-mediated FCV infection. It is indeed plausible that FCV use an alternate receptor in vivo apart from JAM-1, which exhibits tissue-specific distribution. Additionally, FCV attached to soluble junctional adhesion molecule-1 and hemophilic junctional adhesion molecule-1 (sJAM-1 and hJAM-1), and the proliferation of some strains in Vero cells was impeded by the anti-hJAM-1 antibody, indicating that sJAM-1 may possibly function as an FCV receptor [14].

FCV life cycle and conformational change

Two studies have examined the entry pathway of FCV [20, 21]. A more recent study using drugs and dominant inhibitors of different endocytic uptake pathways has confirmed that membrane penetration by FCV requires exposure to a low pH environment during cell entry and has shown that FCV is taken into cells by clathrin-mediated uptake from the plasma membrane (Fig. 2) [20]. The cell membrane becomes permeable to tiny compounds, like the toxin α-sarcin, when FCV binds to cells that are open to it [22] A hole in the cell membrane has been induced by FCV, which could be required for the DNA to be released. The tertiary structure of viral capsids in *Caliciviridae* is conserved, which implies that these viruses could use similar entry mechanisms [12]. The infectivity of FCV isolates varied, which helped to clarify the entrance process. The pure soluble fJAM-A ectodomain is incubated at 37 °C to inactivate VS-FCV viral isolates, including FCV-5. Just like with poliovirus, this feature made it possible to selectively breed soluble receptor resistant (SRR) mutants [23]. 20 distinct capsid alterations in the FCV-5 capsid that are unaffected by incubation with soluble fJAM-A were found using this technique. A suggested explanation for this inactivation involves changes to the capsid's structure that encourage membrane interaction and genome release.

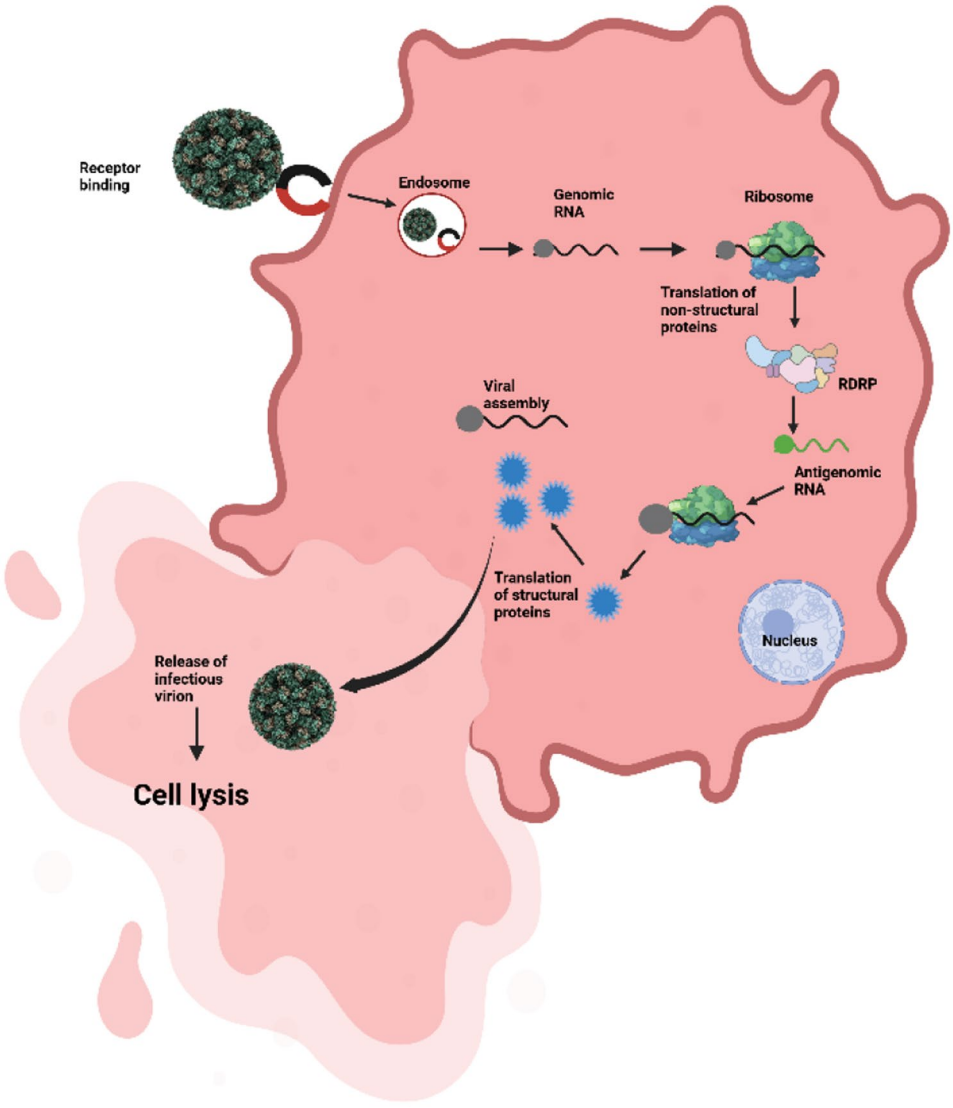

Fig. 2 Lifecycle of FCV. Following receptor engagement, the genome is released by clathrin-mediated endocytosis. The 5′ VPg facilitates the translation of non-structural proteins by interacting with the translational machinery. Antigenomic RNA is transcribed by the viral RNA-dependent RNA polymerase (RDRP) and then used to generate genomic RNA. The infectious virions that are discharged from cells and induce cell lysis are made up of structural proteins and RNA

The soluble receptor causes the FCV-5 virus and SRR mutants to become more hydrophobic, which probably starts the release of the genome [19]. This study utilised mutant viruses picked in tissue culture; hence, mutations in other genomic regions may have affected the altered neutralisation capacity. According to this previous study, it is thought that conformational changes that make the FCV capsid more hydrophobic are necessary for the viral genome to be released from the capsid and for the capsid to attach to membranes. The SRR mutations are G329D, K572E, and V516A and the VP1 domain of the FCV5 capsid encompasses all modifications. An amino acid that is highly conserved across caliciviruses contains the G329D mutation at the P domain-S domain junction. The K572E mutation is hidden at the dimer interface of the capsid architecture and is located within the antigenic domain. The V516A mutation is situated within a surface-exposed loop, placed between two P domains. All of these modifications produce live viruses that demonstrate a variation in hydrophobicity when incubated with fJAM-A. When fJAM-A binds to FCV, a cryo-electron microscopy analysis of the interaction verified that the viral capsid undergoes structural changes [12]. The movement was determined to take place in the S and P domains; however, insufficient resolution impeded the identification of a specific secondary structure associated with the movement. The FCV capsid experiences structural alterations, revealing previously concealed

hydrophobic regions. This conformational change may facilitate the interaction of virus with the cellular membrane. A further conformational change may occur, causing the capsid to embed itself into the membrane and generate a pore, thereby releasing the DNA. The trigger for conformational change in FCV remains unidentified; nonetheless, it may play a crucial role in the progression of VS-FCV. Research demonstrated that VS sickness virus isolates saw a 1000-fold decrease in infectivity after pre-incubation with soluble fJAM-A at 37 °C, whereas non-VS isolates displayed no significant changes. Different temperatures and storage at 4 degrees Celsius exhibited varying effects on infectivity compared to the assessment at 37 degrees Celsius. The viral infectivity is markedly affected by temperature and concentration levels when fJAM-A induces conformational changes [19].

Proteins of FCV

Structural proteins

The basic capsid structure production and host interaction activities rely on VP1 and VP2 joint effort while VP2 facilitates virus assembly and makes the virus infectious. The interaction between VP1 and VP2 ensures the development of functional viral particles with effective infection and replication skills [13]. Scientists have extensively studied the main protein VP1 because of its structural characteristics and antigenic properties yet ongoing research on VP2 helps understand how *calicivirus* builds and matures.

VP1

FCV maintains structural integrity through its component proteins VP1 and VP2 that both support the formation of viral particles as well as their stability while ensuring infectivity. Open reading frame 2(ORF2) define the viral capsid and its RNA content and produces the primary capsid protein VP1. The virus consists mainly of this protein measuring 58–60 kDa in size. This protein exists in 180 identical replications that self-arrange to form 90 double units responsible for creating T = 3 icosahedral symmetry in the capsid. The VP1 protein contains two structural components called Shell (S) domain together with protruding (P) domain. The core layer of the S domain provides structural stability and compaction together with the P domain that forms outer layers which contain two subdomains called P1 and P2 [24]. The P1 subdomain stabilizes the P2 subdomain of fJAM-A while it connects to the host receptor and prevents immunological response to the virus. The P2 subdomain possesses antigenic features derived from neutralizing epitopes which comprise the target of host immune response and draw scientific attention for vaccine development. The P2 subdomain genetic polymorphism enables FCV to adapt to immunological challenges that help both evade immune defenses and create strain variations [4, 17]. VP1 plays multiple crucial roles during the viral life cycle and pathogenic process because it creates viral capsids, attaches to receptors and functions as the main viral antigen and interacts with immune systems.

VP2

The FCV replication process depends on VP2 for its maintenance and progeny viral particles to be released. The viral particle contains either one or two VP2 copies according to predictions and this protein aids in capsid self-assembly. The primary function of VP2 in virions rests in maintaining their stability as well as maturation processes [7]. The development of infectious virions depends crucially on VP2 even though its structure and processes are less well-defined than those of VP1. The formation of viral capsid depends on the VP2 gene because research shows that viruses carrying gene modifications or deletions of VP2 fail to create infectious particles. The viral RNA genome appears to get more packable by VP2 which additionally stabilizes the capsid while exposed to environmental threats [25]. The viral infectivity benefits from VP2 because it helps VP1 properly fold and assemble thus improper particle formation occurs without it.

Function of VP2

VP2 mediates calicivirus RNA genome release

A successful viral infection requires the critical step of genetic material transfer between viruses and host cells at the beginning of infection. Most naked viruses, including *caliciviruses*, have an ambiguous mechanism, which hinders the development of therapeutic medicines that target this crucial phase. VP2 increases FCV RNA releases by penetrating infected cells' endosomal membranes. A novel FCV cell entrance model was introducedin which FCV commences infection by initially binding to its cellular receptor, fJAM-A, on the surface of the host cell. It subsequently enters endosomes via clathrin-dependent endocytosis, releases the gRNA into the cytoplasm via VP2-created pores in the endosome membranes, and initiates genome RNA replication in the cytoplasm. Concurrently, the capsid proteins undergo degradation within the late endosomes (Fig. 3)that enhances our comprehension of *calicivirus* biology [26].

After binding with receptor, most non-enveloped viruses enter cells through endocytosis [27]. The dissemination of the viral genome entails a competitive engagement with the host cell. If this process is excessively sluggish, the virus may infiltrate late endosomes, rendering it vulnerable to destruction by the acidic milieu and proteolytic enzymes, perhaps resulting in an unsuccessful infection [28]. Numerous non-enveloped viruses have evolved mechanisms to influence the endosome,

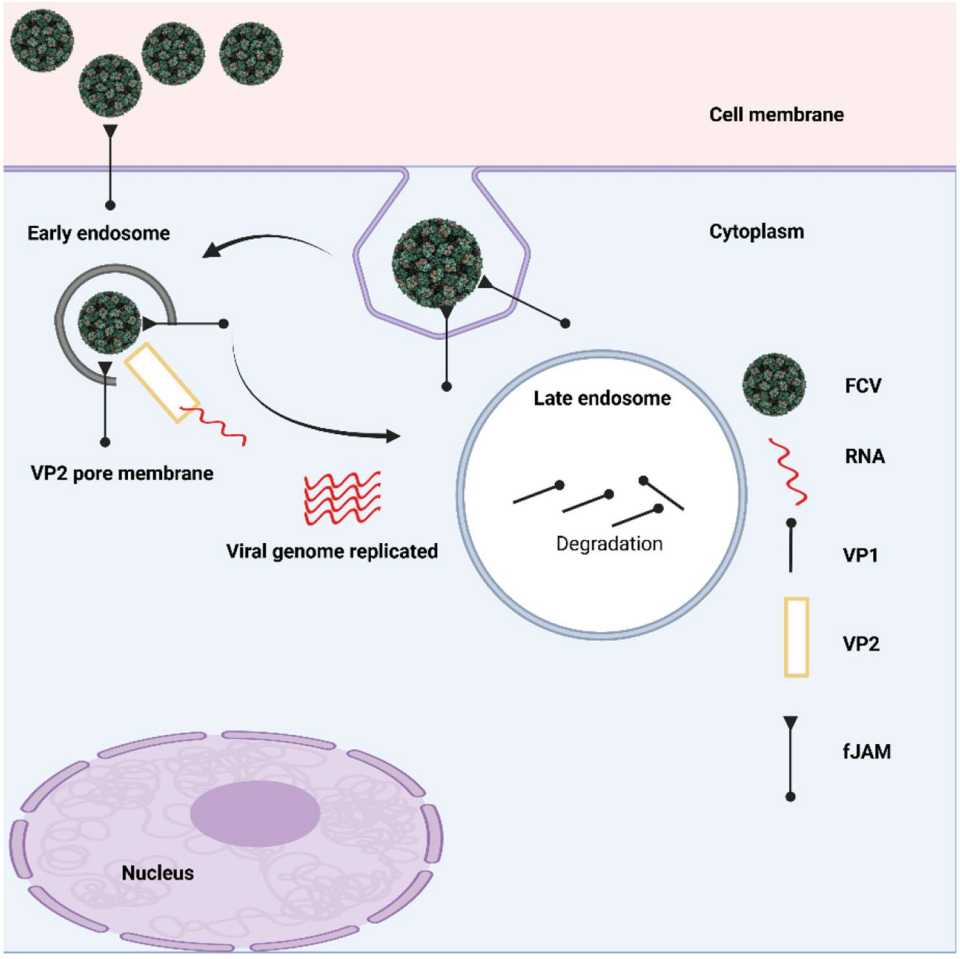

Fig. 3 Schematic representation of VP2 facilitating RNA genome release in *caliciviruses* [26]. By attaching itself on the host cell membrane's fJAM-A, FCV penetrates early endosomes through clathrin-mediated endocytosis. The gRNA enters the cytoplasm and multiplies there after being released via perforations in the early endosome membrane made by VP2. In late endosomes, the viral capsid is broken down

facilitating the entry of their genomes into the cytoplasm at optimal periods. Certain viruses, including FCV, are able to secrete their genomic RNA into the cell fluid during the early stages of endosome maturation. Other viruses, such as human astroviruses and human rhinovirus type 2, translocate to late endosomes, where they depend on the very acidic environment for efficient RNA transfer [29–32].

VP2 is necessary for calicivirus replication and produces port-like structures when it comes into contact with the FCV receptor, It is believed that VP2 serves as the membrane penetration peptide that facilitates FCV to release its gRNA [10, 33]. At pH 6.2, VP2 may attach to and traverse the bilayer membrane of liposomes, resulting in leaking. This process is essentially dependent on hydrophobic N-terminus of VP2. Additionally, modifying the hydrophobic residues in the VP2 N-terminus reduces the rate at which gRNA is released from FCV. These results contribute to the current understanding of *Picornavirus* VP4 [34, 35]. VP2 is thought to serve as a membrane penetration peptide in FCV. Its hydrophobic N-terminus creates small breaches in the early endosome membrane, allowing gRNA to be released.

Nonstructural protein

Nonstructural proteins of FCV are essential for virus replication, genome processing and interaction with the host cell. Unlike structural proteins, they are not part of the virus particle but serve a vital function in viral life cycle regulation. RNA-dependent RNA polymerase (RdRp), 3 C-like protease, helicase (NTPase), and many other poorly understood non-structural proteins called NS1, NS2, and NS4 are among the mature non-structural proteins found in *caliciviruses* [36].

RdRp

The genomes of *caliciviruses* to those of *picornaviruses* and other positive-sense ssRNA viruses were compared in order to assess their protease, helicase, RdRp, and VPg activities [37–39]. For instance, practically a GDD

motif is present in the active region of all RNA polymerases, which is a hallmark of a protein with a conserved domain or motif that signifies function. In the absence of proofreading, the RdRp consistently generates substantial genetic diversity while replicating the viral genome. At the intersection of RdRp and structural protein coding regions, *calicivirus* infected cells frequently undergo template switching which increases genetic diversity even more [40].

Protease

The proteolytic cleavage of the viral polyprotein is facilitated by *calicivirus* protease, which is also known as 3 C-like protease in reference to its *picornavirus* counterpart [41].

Helicase

During viral replication, the calicivirus helicase (like related proteins in other viruses) reacts with ATP to unwind double-stranded RNA intermediates. Nevertheless, the calicivirus helicase serves other purposes as well. It acts as an RNA chaperone and helps with vesicular structure creation, which includes replication complexes, and ATP-independent modification of structured RNA [42, 43].

VPg

Since the VPg protein is present in mature virus particles and covalently binds to the 5' end of both genomic and subgenomic RNAs, it may be considered a structural protein even though it is frequently classified as non-structural. The VPg serves as a primer for the viral genome's replication and is necessary for starting translation in infected cells [44, 45].

NS1/2, NS1, NS2, and NS4

Since these non-structural proteins do not have any sequence homology with other proteins, it is more difficult to ascertain their functions. Within the *Caliciviridae* family, there exists significant sequence variability, rendering non-structural protein sequences ineffective for constructing significant phylogenetic trees, unless they come from viruses that are closely related. On the other hand, phylogenetic studies work considerably better with highly conserved RdRp sequences [46]. The positions of the genes encoding non-structural proteins in the viral genome, on the other hand, are more or less constant. Each calicivirus has NS1/2 coding at the 5' end, followed by the NS4 sequence and finally the helicase sequence. Not every protein in the NS1/2 family is cleaved by proteases. *Vesiviruses*, *lagoviruses*, *neboviruses*, and *sapoviruses* all produce the NS1 and NS2 proteins by efficiently cleaving the NS1/2 precursor protein with the help of viral and/or host cell proteases. The efficiency of cleavage in some viruses is unclear, and there may be more stable precursor proteins [47].

Functions of nonstructural proteins

Autophagy initiation by nonstructural protein

Multiple roles for autophagy have been found in viral infections. Autolysosomes may break down *influenza A virus* (IAV) and human immunodeficiency virus 1 (HIV1) particles, hence autophagy can xenophagically dispose of viral particles [48, 49]. On the other hand, a number of studies have shown that viruses may exploit autophagy as a means of boosting reproduction. The hepatitis C virus and IAV, for example, can restrict full autophagic flow by inhibiting the union of autophagic vesicles and lysosomes, thus enhancing viral reproduction [50–53]. Multiple studies have shown that host autophagy and the virus have a complex and reciprocal connection. FCV infection triggers autophagosome formation and LC3B is recruited to autophagosomal membranes which shows a connection between autophagy and FCV infection. Nonstructural FCV P30, P32, and P39 proteins facilitate the formation of autophagosomes. Even though autophagy can be triggered by FCV infection, more investigation is required to completely comprehend the specific relationships between FCV viral proteins and other elements linked to autophagy.

One study examined how the entire autophagy process contributes to replication of FCV [54]. To ascertain the exact role of autophagy in FCV replication, autophagy inducers and inhibitors were employed. The findings indicated that rapamycin, an autophagy inducer, significantly elevated FCV mRNA levels and FCV titers, whereas ly294002, an early autophagy inhibitor, diminished FCV replication. It has been suggested that FCV replication may be aided during the initial phases of autophagy, which include membrane elongation and autophagosome formation. It is feasible that an intermediate phase between ly294002 suppression and chloroquine inhibition might benefit FCV development but this possibility requires more research.

The endoplasmic reticulum is recognized as the principal biological membrane source of the autophagosome [55, 56]. FCV non-structural proteins P30, P32, and P39 may utilise autophagy-related components of the endoplasmic reticulum to influence the replication complex, potentially increasing viral replication. Chloroquine, a late autophagy inhibitor, boosted FCV replication suggests that late autophagic breakdown might remove FCV virions. Autophagy caused by FCV infection may be multifaceted and potentially beneficial and detrimental at different points in time, according to pre-treatment of various autophagy-related medicines in FCV-infected cells [57]. Numerous studies demonstrate that *calicivirus* infection triggers the innate immune response of

host, while the virus may implement strategic countermeasures. Murine norovirus (MNV) double-stranded RNA (dsRNA) was detected by host MDA5, thereby initiating the interferon response [58]. Proteinases RIG-I and MDA5 are potent inhibitors of human norovirus (HuNoV) infection and its proliferation [59]. Furthermore, the RHDV activates components that respond to interferon [60]. The host immune system has evolved to recognise and destroy *calicivirus* infections, including FCV. Neither Bolin nor HRB-SS nor FCV strain F9 can start the IFN-β response. FCV P39 prevents IRF-3 phosphorylation and the synthesis of IFN-γ and ISG15. The interferon response is suppressed by the FCV strain 2280 P30 by the direct destruction of IFNAR1 mRNA [61].

Counteracting innate immune responses

A wide range of viruses have evolved mechanisms to influence the host immune response by evading IFN-a/b signals. Host defensive responses is downregulated by *calicivirus* nonstructural proteins NS1/2 and NS4. Viruses frequently circumvent host immune responses by modulating host cell transcriptional activity. A transcriptome investigation of transiently transfected monocytes demonstrated that norovirus NS1/2 promotes a pro-apoptotic phenotype, enhances the production of many pro-inflammatory cytokines and chemokines, and reduces the expression of toll-like receptors (TLR)-4, -7, -8, and − 9. This suggests that both innate and adaptive immune responses are regulated by the *norovirus* NS1/2 protein [62]. Additionally, protein-level innate immune responses may be impacted by norovirus NS1/2. It is suggested that *caliciviruses* regulate intracellular trafficking by the association of *norovirus* NS1/2 with vesicle-associated membrane protein VAP-A. Critical innate immunity proteins including TLRs, IFNs, and MHCs would not be able to reach the cell surface in this case.

The NS4 (p30) protein, a homolog of *picornavirus* 3 A, is responsible for impairing host cell innate immune responses in FCV. The IFN signaling in pre-treated FCV-infected cells was examined utilising the transcription inhibitor *actinomycin* D to impede virus-induced transcription. The mRNA levels of the IFN-α/β receptor subunits 1 and 2 (IFNAR1 and IFNAR2) were analysed, revealing a considerably decreased half-life of IFNAR1 mRNAs in cells infected with viruses compared to control cells (6.3 vs. 100 h, respectively). As a result, FCV prevents the production of an active IFN type I receptor by causing its mRNA to degrade [61]. To determine the protein implicated in IFNAR1 mRNA degradation, cells were transiently transfected with certain FCV nonstructural proteins, and IFNAR1 mRNA levels were measured. The only protein that had a substantial impact on the stability of the IFNAR1 mRNA was NS4 [61].

To get around innate immune responses, *caliciviruses* have developed a number of strategies. More counter defense mechanisms probably exist, but their identification is currently hampered by weak cell culture models and replication procedures.

Conclusion and future perspectives

Research into *Feline calicivirus* structural and nonstructural proteins has improved both our knowledge of viral pathogenesis and host interactions together with discovery of new therapeutic targets. Research on capsid protein mechanisms, immune evasion, replication, and host regulation has advanced our understanding of FCV infection pathways. The findings generated significant real-world value for vaccine development together with antiviral strategies. Studies on caliciviruses, including human norovirus and rabbit hemorrhagic disease virus, have revealed common structural features and functional domains, providing significant insights into virus transmission across species. Multipurpose structural biology equipment, along with molecular research tools from analogous viruses, has substantially improved research on FCV. A structural analysis of understudied nonstructural proteins, in conjunction with the examination of their functional behavior during viral infection cycles, is necessary to advance the field of research. Scientific progress in the field of antiviral medicine and vaccine development is dependent on the use of high-throughput screening technology and comparative virology approaches. The continuous study of FCV viruses alongside other *caliciviruses* will develop our understanding of viral pathogenesis allowing benefits for feline health as well as virological research.

Abbreviations

FCV	Feline calicivirus
VS-FCV	Virulent systemic-feline calicivirus
RdRp	RNA dependent RNA polymerase
ORF	Open reading frame
fJAM	Feline junctional adhesion molecule
PCC	Primary chicken cecal cells
RK	Rabbit kidney
EPC	Epithelioma papulosum cyprini
FHM	Fathead minnow
CHSE-214	Chinook salmon embryo
BF-2	Bluegill fry
RTG-2	rainbow trout gonad cell lines
HBGA	Histo-blood group antigen
MDBK	Madin–Darby Bovine Kidney
BIE cells	Bovine intestinal epithelial cell line
SAs	Sialic acids
LLC-PK cells	Pork kidney epithelial cells
HIE	Human enteroids cell
h-iPSC–derived IECs	Human Induced Pluripotent Stem Cell-Derived Intestinal Epithelial Cells
BV-2	Mouse derived microglial cell line
RAW	Mouse macrophagic cell line
TIBs	Tumor-infiltrating B cells
Vero E6 cells	African green monkey kidney cells
LLC-MK2	Rhesus monkey kidney

Author contributions
Sana Asif: Conceptualization, writing the original draft, preparing the figures, reviewing, and editing. Deng Yingkun: Conducted the literature review and contributed to drafting the manuscript. Chunchun Meng: Conceptualized, supervised, thoroughly reviewed, and provided valuable feedback. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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