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Immune evasion in classical swine fever: Viral modulation of antigen–presentation pathways

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ABSTRACT

Classical swine fever remains a major threat to global pig production systems, despite decades of sustained control endeavours. Its causative agent classical swine fever virus (CSFV) employs a highly coordinated set of immune evasion mechanisms to weaken host antiviral defences and permit extensive viral replication. A central focus of this strategy is the antigen-presentation machinery, where CSFV disrupts both major histocompatibility complex class (MHC)-I and MHC-II pathways in macrophages and dendritic cells, which are its primary immune cell reservoirs. By suppressing interferon signaling, dysregulating NF- κ B activation, and impairing the maturation of antigen-presenting cells, CSFV compromises peptide processing, co-stimulatory signaling, and T-cell priming. These defects propagate through the adaptive immune system, leading to delayed cytotoxic responses, inadequate CD4⁺ T-cell help, and impaired humoral immunity. CSFV simultaneously reshapes macrophage polarization, drives profound dendritic cell dysfunction, induces lymphoid apoptosis, and modulates $\gamma\delta$ T-cell activity in a manner that correlates with viral virulence. In addition, viral remodeling of intracellular organelles further limits antigen presentation and exacerbates immunopathology. Together, these interconnected mechanisms create a permissive cellular environment that facilitates viral persistence and amplifies disease severity. Understanding how CSFV manipulates antigen-presentation pathways provides crucial insights for the design of next-generation vaccines and therapeutic strategies capable of restoring robust antiviral immunity.

KEYWORDS: Adaptive immunity suppression; Antigen presentation; Classical swine fever; Immune evasion; Macrophages; Dendritic cells

1. Introduction

Classical swine fever (CSF) remains a major threat to global pig production systems, despite decades of sustained control endeavours. The etiological agent, classical swine fever virus (CSFV), is an enveloped, positive-sense RNA virus belonging to the genus *Pestivirus*. What makes CSF particularly intractable is not only the contagiousness of the virus but also its ability to induce a profound and multifaceted state of immunosuppression[1]. Young pigs often succumb rapidly to infection, whereas survivors or those with mild clinical manifestations may carry and shed the virus for prolonged periods, thereby sustaining transmission cycles in both domestic and wild pig populations. A hallmark of CSFV infection is the disruption of the host's adaptive immune machinery[2]. Effective antiviral immunity depends on the seamless operation of antigen-presentation pathways, mechanisms through which antigen-presenting cells (APCs) detect, process, and present viral peptides to T lymphocytes. This process is central to the activation of cytotoxic CD8⁺ T cells, the orchestration of CD4⁺ T-cell-mediated immune regulation, and the development of a robust humoral response. However, growing evidence indicates that CSFV systematically undermines multiple components of these pathways, manipulating the host's immune

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microenvironment to facilitate viral persistence[3,4].

CSFV targets a range of APCs, including dendritic cells (DCs), macrophages, and B cells, impairing their maturation, altering cytokine secretion profiles, and reducing their antigen-presenting capacity. The virus interferes with both major histocompatibility complex (MHC)-I and MHC-II antigen-processing pathways, hindering peptide loading, compromising surface expression, and inhibiting signals required to prime naïve T cells. Beyond classical MHC molecules, CSFV also modulates nonclassical antigen-presentation systems and costimulatory signals such as CD80 and CD86, further diminishing the quality and intensity of T-cell activation. These immunomodulatory effects do not act in isolation. CSFV simultaneously modulates innate immune sensors, suppresses interferon (IFN) production, interferes with nuclear factor kappa B (NF- κ B) activation, and reshapes the intracellular environment through organelle stress and metabolic reprogramming[5–7]. These early events shape subsequent adaptive responses; when APC function is compromised at the onset of infection, the entire immune cascade is weakened, leaving the host unable to mount an effective antiviral defence. Consequently, the virus gains a critical window for replication, systemic dissemination, and induction of immunopathology. Understanding how CSFV manipulates antigen-presentation pathways provides crucial insights into its virulence strategies. It also elucidates why traditional vaccines may fail to confer sterilizing immunity in certain settings and why persistent infections persist even in vaccinated populations. By piecing together the molecular and cellular events underlying this immunomodulation, researchers can better identify vulnerabilities in the viral life cycle and design immune interventions that bypass or counteract these evasion mechanisms[3,8,9]. This review synthesizes current knowledge on CSFV-induced alterations in antigen presentation, highlighting key viral determinants, cellular targets, and downstream consequences for host immunity. A clearer understanding of these virus-host interactions will not only deepen our comprehension of CSFV pathogenesis but also inform the development of next-generation vaccines and immune-restorative therapeutics.

2. Antigen presentation in CSFV infection

Antigen presentation is a key determinant of antiviral immunity during CSFV infection. CSFV antigens normally enter the MHC-I pathway through proteasomal degradation and transporter associated with antigen processing (TAP)-mediated peptide loading, activating cytotoxic CD8⁺ T cells. However, CSFV suppresses this process by downregulating TAP1/TAP2, β 2-microglobulin, and surface MHC-I molecules, thereby limiting cytotoxic T lymphocyte (CTL) recognition. Viral proteins, especially N^{pro}, further inhibit

IFN signaling, which indirectly impairs the efficiency of antigen-processing. Simultaneously, CSFV disrupts the MHC-II pathway in macrophages and DCs, which are its primary target cells. Infected APCs show impaired maturation, reduced MHC-II molecules and co-stimulatory molecules, and weakened cytokine responses, resulting in inadequate CD4⁺ T cell activation. This broad inhibition of antigen presentation contributes to the virus's immunosuppressive phenotype, facilitating its systemic spread and persistence. Insights into these mechanisms are crucial for design of vaccines capable of overcoming CSFV-driven immune modulation[10–13].

3. Central role of macrophages in CSFV pathogenesis

Macrophages are the principal target cells of CSFV and play a pivotal role in shaping both viral pathogenesis and host immune responses. CSFV efficiently infects tissue macrophages and monocyte-derived macrophages, using them as major replication sites that facilitate early viral amplification and systemic dissemination. Infection profoundly alters macrophage function: CSFV suppresses key antiviral pathways, including type I IFN production through N^{pro}-mediated degradation of IRF3, and modulates cytokine secretion by skewing responses toward an anti-inflammatory profile. Critically, CSFV-infected macrophages exhibit impaired antigen presentation, characterized by reduced MHC-II expression, diminished co-stimulatory molecules, and weakened ability to prime T cells. These defects contribute to the profound immunosuppression observed during acute CSF. In addition, macrophage dysfunction drives lymphoid depletion, vascular damage, and hemorrhagic lesions through excessive production of pro-inflammatory mediators such as TNF- α and IL-1 β , alongside dysregulated chemokine signaling. Thus, macrophages act as both viral reservoirs and key mediators of immunopathology, making them central to CSFV virulence, persistence, and disease outcome[14–16].

4. Inhibition of IFN signaling by CSFV

CSFV employs multiple strategies to antagonize the host IFN system, a key antiviral defence pathway. The viral N^{pro} protein is the primary antagonist of type I IFN induction; it targets IRF3 and IRF7 for proteasomal degradation, preventing their activation and nuclear translocation. This mechanism inhibits transcription of *IFN- α/β* genes at the earliest stage of infection. Additionally, the structural protein E^{ms}, with intrinsic RNase activity, degrades extracellular viral RNA, thereby reducing activation of toll-like receptor (TLR) 3 and other pathogen recognition receptors. CSFV further interferes with downstream IFN signaling by disrupting the JAK-STAT pathway, which impairs the phosphorylation and nuclear migration of STAT1

and STAT2 and suppresses assembly of the ISGF3 transcription complex. Consequently, the expression of IFN-stimulated genes, which are central to controlling viral replication, is markedly reduced in CSFV-infected cells. This comprehensive inhibition of IFN induction and signaling enables CSFV to evade innate immune surveillance, facilitating viral replication, systemic dissemination, and the severe immunosuppression that are characteristics of acute CSF pathogenesis[17–20].

5. NF- κ B pathway modulation by CSFV to facilitate immune evasion

CSFV strategically modulates the NF- κ B signaling pathway to evade host immunity surveillance and exacerbate disease progression. Under physiological conditions, viral RNA activates pattern-recognition receptors (PRRs), which trigger inhibitor of kappa-B degradation and NF- κ B nuclear translocation, thereby initiating the transcription of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6. CSFV interrupts this signaling cascade by suppressing upstream PRR signaling and altering the NF- κ B activation in infected immune cells, particularly macrophages and DCs. Several CSFV proteins are involved in this regulatory process. N^{pro} dampens NF- κ B activation indirectly by impairing IRF signaling pathways (Table 1) and desensitizing PRR responses, while E^{ms} degrades extracellular viral RNA to attenuate TLR3-mediated inflammatory signaling[15,18,21]. In macrophages, CSFV induces a partial or transient NF- κ B activation. This insufficient activation fails to mount an effective antiviral response but drives aberrant cytokine production. This skewed activation suppresses robust inflammatory response required for viral clearance while simultaneously exacerbating pathological outcomes such as lymphoid depletion, vascular injury, and hemorrhage. Rather than completely blocking NF- κ B activity, CSFV fine-tunes its activation to establish an immunosuppressive microenvironment characterized by weakened antiviral signaling, impaired antigen presentation, and excessive but ineffective inflammation. This targeted modulation enables viral persistence, aggravates immunopathology, and constitutes a key molecular mechanism responsible for the severe clinical manifestations of CSF[2,15,22,23].

6. Dual roles of CSFV in apoptosis regulation

CSFV employs a biphasic strategy to modulate apoptosis, acting as either an inhibitor or inducer of programmed cell death depending on the infection stage and the target cell type. At early phase of infection, CSFV predominantly inhibits apoptosis to

ensure efficient viral replication and persistent infection. This anti-apoptotic activity is mediated by viral proteins such as N^{pro}, which suppresses IFN responses and stabilizes cellular survival pathways, as well as the E^{ms} RNase, which restricts innate immune activation. Infected macrophages and DCs show attenuated caspase activation and preserved mitochondrial integrity, enabling prolonged viral replication[2,24]. In contrast, at the late stage of infection, CSFV can promote apoptosis, particularly in lymphoid tissues, thereby driving the characteristic immunopathology of CSF[25]. Excessive secretion of inflammatory mediators (*e.g.*, TNF- α , IL-1 β) by dysregulated macrophages, combined with direct viral effects, triggers activation of caspase-dependent apoptotic pathways in lymphocytes. This leads to massive lymphoid depletion, immune suppression, and extensive tissue damage. Additionally, by inducing apoptosis in bystander immune cells while sparing primary viral replication niches, CSFV facilitates immune evasion and systemic viral dissemination[26,27].

7. Macrophages in CSFV infection: A double-edged sword in antiviral defence and immunopathology

Macrophages are central to both the protective and pathological outcomes of CSFV infection. As frontline innate immune cells, macrophages detect viral invasion through PRRs and initiate antiviral defences by secreting type I IFNs, pro-inflammatory cytokines, and chemokines (Figure 1). They also act as key APCs, linking innate and adaptive immune responses[15]. However, CSFV disrupts NF- κ B signaling and impairs antigen presentation by downregulating MHC molecules and co-stimulatory factors[28]. These changes cripple the antiviral capacity of macrophage, allowing the virus to replicate with minimal immune resistance. At the same time, CSFV has evolved a strong tropism for macrophages, using them as primary replication niches and reprogramming cellular functions to favor viral persistence. Once infected, macrophages undergo profound functional remodeling. CSFV suppresses IFN production; CSFV-infected macrophages become major drivers of immunopathology. Dysregulated release of TNF- α , IL-1 β , IL-6, and chemokines sustains systemic inflammation, endothelial injury, thrombocytopenia, and the typical hemorrhagic lesions of acute CSF. In lymphoid tissues, macrophage-derived mediators trigger extensive lymphocyte apoptosis, exacerbating the severe immunosuppression during infection. Thus, macrophages act as a double-edged sword in CSFV pathogenesis: they are essential for antiviral defence yet are hijacked by CSFV to propagate immune dysfunction and tissue damage[15,29]. This functional duality highlights macrophages as critical targets for developing optimized vaccines and antiviral strategies aimed at restoring immune homeostasis and alleviating CSFV-induced pathology.

Table 1. CSFV immune evasion mechanisms: Viral protein interference with IRF, NF- κ B, and interferon signaling pathways.

Viral protein	Classification (Structural / NS)	Primary host target(s)	Innate immune pathway inhibited	Molecular mechanism of antagonism	Type of IFN affected	Experimental evidence	Ref
N ^{pro}	Non-structural	IRF3	RLR-IRF3 pathway (IFN- α/β induction)	Binds IRF3 $\rightarrow$ triggers ubiquitination $\rightarrow$ proteasomal degradation $\rightarrow$ blocks IRF3 phosphorylation & nuclear entry $\rightarrow$ eliminates IFN- β transcription	Type I IFN (IFN- α , IFN- β)	IRF3 degradation in infected cells; N ^{pro} -mutant viruses induce strong IFN; co-IP and ubiquitination assays	[17,20]
N ^{pro}	Non-structural	IRF1	IRF1-IFN- λ induction axis	Reduces IRF1 mRNA & protein levels; blocks IRF1 nuclear translocation $\rightarrow$ decreases type III IFN gene transcription	Type III IFN (IFN- λ 1/ λ 3)	Luciferase reporters, IRF1 overexpression rescue experiments	[59]
NS4B	Non-structural	TBK1; IRF3; NF- κ B pathway components	RIG-I/MDA5- TBK1-IRF3/NF- κ B	Interacts with TBK1 $\rightarrow$ inhibits phosphorylation & activation of IRF3; reduces NF- κ B p65 activation; decreases IL-8 and IFN- β transcription	Type I IFN	Co-IP TBK1- NS4B; phosphorylation assays; NS4B- expressing cells show reduced IRF3 activity	[58]
NS4B	Non-structural	Mitochondrial membranes	RLR signaling platform disturbance	Alters mitochondrial morphology & MAVS signaling environment	IFN- β	Confocal microscopy; mitochondrial potential studies	[7]
NS5A	Non-structural	NEMO (IKK γ)	NF- κ B signaling pathway	Binds NEMO $\rightarrow$ induces ubiquitin-mediated proteasomal degradation $\rightarrow$ blocks IKK activation $\rightarrow$ suppresses NF- κ B- driven IFN- β transcription	Type I IFN (IFN- β)	NEMO degradation assays; NF- κ B luciferase reporter assays; NS5A- mutant viruses show restored IFN induction	[20,53]
NS5A	Non-structural	PKR & JAK/ STAT regulators (proposed)	Possible inhibition of ISG induction	Reduces PKR activation & downstream ISG transcription (strain dependent; still under study)	IFN- α/β downstream signaling	Overexpression assays; phosphorylation analysis	[3]
E ^{ms} (E0)	Structural (secreted & membrane-bound glycoprotein)	Extracellular dsRNA; TLR3	TLR3-TRIF pathway (PAMP sensing)	RNase activity degrades dsRNA $\rightarrow$ prevents TLR3 activation $\rightarrow$ blocks IFN- β promoter and ISG expression	Type I IFN (IFN- β)	RNase-dead mutants fail to suppress IFN; dsRNA degradation assays	[49]
E ^{ms} (E0)	Structural	Cationic host RNA- binding proteins	Prevents extracellular RNA sensing	Sequestration of dsRNA by surface Erns; immune decoy function	IFN- β	Evidence from RNase-resistant binding assays	[7]
E2 (envelope glycoprotein) (partial evidence)	Structural	TLR2/innate receptors	Modulation of cytokine signaling	Some studies suggest interference with TLR2 activation and macrophage signaling	Indirect IFN effects	<i>In vitro</i> macrophage assays	[18]
Core protein (C protein) (emerging evidence)	Structural	IFN promoter regulators	Interference with IRF-NF- κ B crosstalk	Proposed reduction in IFN promoter activation; still being validated	Type I IFN	Reporter assays only (not fully validated in viral context)	[3]

CSFV: classical swine fever virus; N^{pro}: N-terminal autoprotease; E^{ms}: envelope ribonuclease glycoprotein; E2: envelope glycoprotein 2; NS: non-structural protein; IRF1: interferon regulatory factor 1; IRF3: interferon regulatory factor 3; RLR: RIG-I-like receptor; RIG-I: retinoic acid-inducible gene I; MDA5: melanoma differentiation-associated protein 5; TLR2: toll-like receptor 2; TLR3: toll-like receptor 3; TRIF: TIR-domain-containing adapter-inducing interferon- β ; PAMP: pathogen-associated molecular pattern; dsRNA: double-stranded RNA; RNase: ribonuclease; MAVS: mitochondrial antiviral signaling protein; TBK1: TANK-binding kinase 1; NF- κ B: nuclear factor kappa B; NEMO (IKK γ): NF- κ B essential modulator (I κ B kinase gamma); IKK: I κ B kinase; PKR: protein kinase R; JAK/STAT: Janus kinase/signal transducer and activator of transcription; ISG: interferon-stimulated gene; IFN: interferon; IFN- α : interferon alpha; IFN- β : interferon beta; IFN- λ : interferon lambda; IL-8: interleukin-8; mRNA: messenger RNA; co-IP: co-immunoprecipitation.

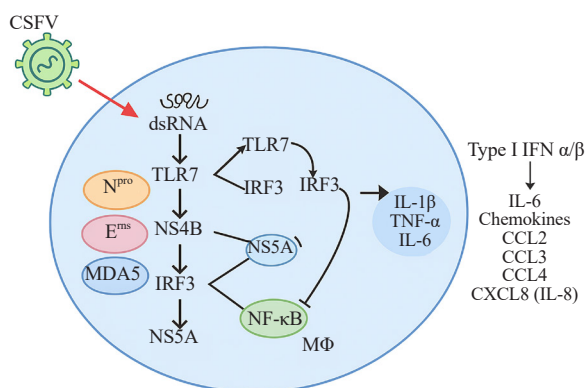


Figure 1. Impact of classical swine fever virus (CSFV) infection on macrophage (MΦ) innate immune responses. N^{pro}: N-terminal autoprotease; E^{ms}: envelope ribonuclease glycoprotein; IRF3: interferon regulatory factor 3; MDA5: melanoma differentiation-associated protein 5; TLR7: toll-like receptor 7; dsRNA: double-stranded RNA; NF-κB: nuclear factor kappa B; IFN: interferon; IL: interleukin; NS: non-structural protein; CCL: C-C motif chemokine ligand; CXCL8: C-X-C motif chemokine ligand 8.

8. CSFV interaction with macrophage polarization phenotypes

Macrophage polarization profoundly influences the outcome of CSFV infection. Macrophages can adopt either pro-inflammatory M1 or regulatory M2 phenotypes, each with distinct antiviral capabilities and immunomodulatory properties[30,31]. CSFV exploits this phenotypic plasticity by selectively manipulating macrophage polarization to support viral replication and blunt protective immune responses. M1 macrophages, characterized by high levels of type I IFNs, nitric oxide, and pro-inflammatory cytokines, generally exert strong antiviral activity. However, CSFV infection suppresses M1-associated signaling pathways by inhibiting IRF3-mediated IFN induction, downregulating NF-κB activation, and impairing antigen-presenting functions. This reduces the antiviral competence of M1 macrophages and prevents robust clearance of virus-infected tissues. Conversely, CSFV promotes the induction or maintenance of M2-like polarization, which is marked by elevated expression of IL-10, TGF-β, and arginase-1. M2 macrophages create a permissive microenvironment for viral replication by suppressing inflammatory responses, inhibiting T-cell activation, and promoting tissue repair-associated programs that benefit viral persistence. Studies demonstrate that CSFV-infected macrophages exhibit transcriptional profiles reminiscent of M2-like states, including impaired co-stimulatory molecule expression and attenuated IFN responses[32,33]. By skewing macrophage polarization away from antiviral M1 functions and toward immunoregulatory M2 phenotypes, CSFV creates a microenvironment that both supports viral survival and contributes to systemic immune suppression. This dynamic interaction between CSFV infection and macrophage phenotypic plasticity is a key determinant of CSFV pathogenesis and represents

a potential target for the development of immunomodulatory therapies and next-generation vaccines[34].

9. Impact of CSFV on DCs antigen presentation

DCs are central regulators of antiviral immunity, but CSFV profoundly impairs their antigen-presenting capacity to weaken host defence. CSFV infects both conventional and plasmacytoid DC subsets, leading to impaired maturation, reduced expression of MHC-I/MHC-II, and downregulation of key co-stimulatory molecules such as CD80/86. These alterations directly compromise the DC's ability to prime naïve T cells and initiate robust adaptive immune responses[5,15,35,36]. CSFV also inhibits innate sensing pathways in DCs. Viral proteins such as N^{pro} suppress type I IFN production by targeting IRF3/IRF7, while E^{ms}, with its RNase activity, attenuates activation of TLR-mediated signaling cascades. This results in reduced secretion of cytokines and chemokines, further impairing T-cell activation and hindering DC migration to lymphoid tissues. Additionally, CSFV-infected DCs display altered metabolic and transcriptional profiles consistent with a tolerogenic or immunosuppressive phenotype, which promotes an ineffective immune microenvironment conducive to viral persistence[37–39]. Through these coordinated mechanisms blocking DC maturation, suppressing IFN responses, impairing antigen presentation, and inhibiting T-cell priming, CSFV transforms DCs from potent initiators of antiviral immunity into dysfunctional immune cells that facilitate immune evasion and systemic viral dissemination.

10. CSFV subverts B-cell function to evade humoral immunity

CSFV employs multiple strategies to impair B-cell activation, antibody production, and the development of long-lasting humoral immunity. Although B cells are not major targets for productive infection, CSFV profoundly alters their functional microenvironment through effects on macrophages, DCs, and lymphoid architecture. Early in infection, CSFV-induced suppression of DC maturation and type I IFN responses leads to weak T-helper cell support, resulting in suboptimal B-cell activation and delayed antibody secretion. CSFV also drives lymphoid depletion, particularly in the spleen and lymph nodes, where massive apoptosis of B cells and supporting stromal cells disrupts germinal center formation[2,40]. This prevents effective affinity maturation and immunoglobulin class switching. In addition, viral modulation of cytokines such as elevated IL-10 and reduced IL-12 skews the immune microenvironment toward a regulatory state that suppresses B-cell proliferation and plasma cell differentiation. Impaired antigen presentation by virus-infected APCs further limits the availability of costimulatory signals required for mounting

robust humoral responses. Even after seroconversion, CSFV's immunomodulatory activities can dampen neutralizing antibody titers and delay development of protective immunity, contributing to viral persistence and facilitating viral spread. By simultaneously hindering B-cell activation, damaging lymphoid tissue structure, and weakening T-helper cell support, CSFV effectively subverts humoral immunity and enhances its capacity for immune evasion[5,8,41].

11. $\gamma\delta$ T cells in CSFV infection: Virulence-linked immune modulation

$\gamma\delta$ T cells play a critical role in early antiviral defence, bridging innate and adaptive immunity, but CSFV modulates their activity in a manner that correlates with viral virulence[42]. In healthy swine, $\gamma\delta$ T cells rapidly respond to viral infection by secreting IFN- γ , enhancing macrophage activation, and contributing to cytotoxic clearance of infected cells. However, during CSFV infection, particularly with highly virulent strains, these functions become profoundly dysregulated. CSFV alters $\gamma\delta$ T-cell frequency, activation status, and cytokine secretion. Highly pathogenic CSFV strains induce $\gamma\delta$ T-cell functional exhaustion characterized by reduced production of IFN- γ and TNF- α , impaired cytotoxicity, and altered expression of activation markers such as CD25 and CD69[43–45]. This suppression is driven indirectly by CSFV-mediated dysfunction of APCs, excessive IL-10 secretion, and widespread lymphoid damage. In contrast, low-virulence CSFV strains may elicit a more controlled $\gamma\delta$ T-cell response that contributes to viral containment, highlighting a strain-dependent pattern of CSFV-induced immunomodulation. Additionally, $\gamma\delta$ T cells accumulate in inflamed lymphoid tissues during acute infection, where their dysregulated activation contributes to the development of immunopathology, including lymphoid depletion and cytokine imbalance. Thus, $\gamma\delta$ T-cell responses during CSFV infection represent a virulence-linked immunomodulatory target, with high-virulence strains suppressing their antiviral functions while simultaneously exploiting inflammatory dysregulation to enhance disease severity[46,47].

12. CSFV-mediated suppression of antigen presentation and adaptive immunity

CSFV employs a multifaceted strategy to disrupt antigen presentation, thereby weakening adaptive immune responses and promoting viral persistence. Infected macrophages and DCs, key APCs, exhibit reduced expression of MHC-I, MHC-II, and essential co-stimulatory molecules such as CD80/86. This suppression stems from CSFV-mediated inhibition of type I IFN signaling, impaired NF- κ B activation, and direct interference of viral proteins

such as N^{pro} and E^{ns} with pathogen-recognition pathways. As a result, APCs fail to efficiently process and present viral peptides to CD8⁺ cytotoxic T cells and CD4⁺ helper T cells[48–50]. Beyond quantitative reductions in antigen presentation molecules, CSFV alters APC functionality at multiple levels. The virus dampens antigen uptake, disrupts endosomal lysosomal processing, and skews APCs toward a tolerogenic or M2-like phenotypic profile that favors anti-inflammatory signaling cascades. These dysfunctional APCs exhibit impaired T-cell priming capacity, leading to delayed or blunted activation of both cellular and humoral arms of adaptive immunity. In lymphoid tissues, extensive apoptosis and architectural damage further diminish antigen presentation niches, compounding the overall immunosuppressive microenvironment. Through this coordinated disruption of antigen processing, MHC expression, co-stimulation, and APC maturation, CSFV effectively impairs the generation of robust T-cell-mediated and antibody-mediated responses. This blockade of antigen presentation is a central mechanism of CSFV immune evasion and a major contributor to the profound immunosuppression observed during acute disease[2,51,52].

13. CSFV-mediated MHC dysregulation and adaptive immune evasion

CSFV targets MHC pathways as a central immune-evasion strategy, undermining both CD8⁺ and CD4⁺ T-cell-mediated immune responses. In macrophages and DCs, CSFV downregulates surface expression of MHC-I molecules by suppressing key components of the antigen-processing machinery, including TAP1/TAP2, β 2-microglobulin, and proteasome-mediated peptide generation. This reduction in MHC-I peptide loading severely limits CTL recognition of infected cells, enabling unimpeded viral replication. CSFV also disrupts MHC-II expression and function, which compromised the ability of APCs to activate CD4⁺ T-helper cells. Viral inhibition of IFN signaling, combined with altered NF- κ B activity and defective DC maturation, reduces transcription and surface expression of MHC-II molecules as well as their associated co-stimulatory proteins. Consequently, infected APCs exhibit diminished antigen uptake and processing capabilities, producing weak or incomplete T-cell priming. Through coordinated suppression of both MHC-I and MHC-II pathways, CSFV effectively cripples the adaptive immune response. Reduced CTL activity, impaired helper T-cell support, and delayed antibody production together create a profoundly immunosuppressed microenvironment that favors viral persistence and systemic dissemination. Disruption of MHC-mediated antigen presentation, therefore, represents a core mechanism by which CSFV subverts host immunity and enhances virulence[53–57].

14. CSFV suppression of MHC-I antigen presentation

CSFV strategically suppresses the MHC-I antigen-presenting pathway to evade CTL surveillance. In infected macrophages and DCs, CSFV interferes with the generation and loading of antigenic peptides by reducing proteasomal processing efficiency and downregulating key components of the peptide transport machinery, including TAP1, TAP2, and β 2-microglobulin. This disruption limits the availability of viral peptides for incorporation into MHC-I complexes. Additionally, CSFV decreases the transcription and surface expression of MHC-I molecules, partly through inhibition of type I IFN signaling and impaired JAK-STAT activation. As a result, fewer MHC-I-peptide complexes reach the cell surface, leading to suboptimal recognition of virus-infected cells by $CD8^+$ T cells (Figure 2). The combined suppression of viral peptide production, peptide transport, and MHC-I expression weakens CTL-mediated cytotoxicity and promotes viral persistence. By downgrading the MHC-I antigen-presenting pathway, CSFV effectively masks infected cells from adaptive immune detection, contributing to systemic viral dissemination and the profound immunosuppression that characterizes acute CSF[3,58–60].

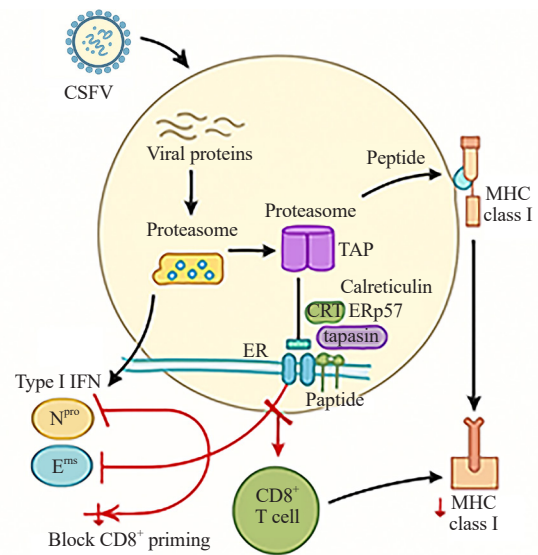


Figure 2. CSFV-mediated modulation of the major histocompatibility complex (MHC) class I antigen presentation pathway and $CD8^+$ T-cell priming. CRT: calreticulin; ER: endoplasmic reticulum; TAP: Transporter associated with antigen processing.

15. CSFV suppression of MHC-II antigen presentation

CSFV profoundly suppresses the MHC-II antigen-presenting pathway, crippling the host's ability to mount effective $CD4^+$ T-cell responses. Infected macrophages and DCs, the primary APCs, exhibit reduced transcription and surface expression of MHC-II molecules, as well as diminished levels of essential co-stimulatory proteins such as CD80/86. This downregulation stems largely from CSFV-mediated inhibition of type I IFN signaling, interference with NF- κ B-driven APC maturation pathways, and the tolerogenic reprogramming of APC phenotypes. CSFV further disrupts the intracellular machinery required for MHC-II antigen loading[2,61,62]. The virus alters endosomal acidification, impairs peptide processing, and affects the expression of HLA-DM-like chaperones, which are responsible for exchanging class II-associated invariant chain peptide for antigenic peptides. As a result, infected APCs present fewer viral peptides and demonstrate a markedly reduced capability to activate naïve $CD4^+$ T cells. By compromising MHC-II expression (Figure 3), peptide loading efficiency and APC maturation, CSFV effectively weakens helper T-cell priming, leading to poor B-cell activation, delayed antibody responses, and broad suppression of adaptive immune. This targeted disruption of the MHC-II pathway is a key mechanism by which CSFV establishes persistent infection and enhances disease severity[5,63].

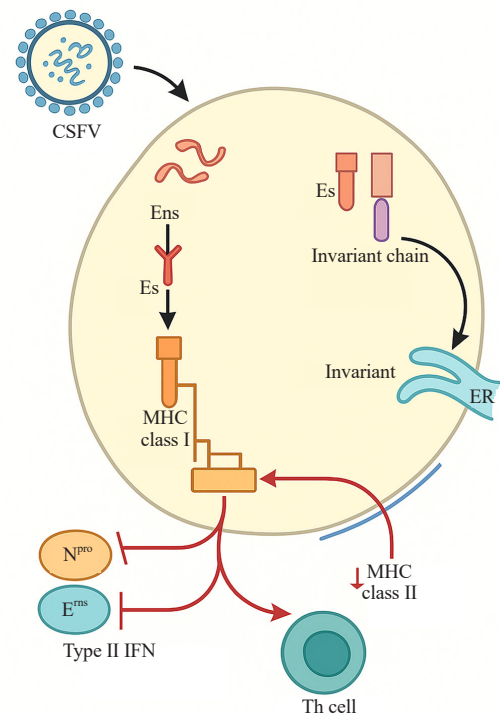


Figure 3. CSFV-mediated modulation of the MHC class II antigen presentation pathway and $CD4^+$ T-helper cell activation.

16. CSFV-mediated dysregulation of CD80/86 signaling

CSFV strategically modulates the expression of co-stimulatory molecules CD80 and CD86 on APCs to impair T-cell activation and facilitate immune evasion. Infected DCs and macrophages display

markedly reduced surface levels of CD80/86, a consequence of CSFV-driven suppression of IFN signaling, downregulated NF- κ B activation, and impaired APC maturation[64]. Since CD80/86 provide the essential “second signal” required for full T-cell activation *via* engagement with CD28 receptor on T cells, their reduction results in suboptimal priming of both CD4⁺ helper T lymphocytes and CD8⁺ CTLs. Beyond simply limiting co-stimulatory signaling, CSFV skews APCs toward a tolerogenic phenotype characterized by increased IL-10 secretion, reduced inflammatory cytokine release, and diminished antigen-presenting capability[5,65]. This tolerogenic microenvironment promotes T-cell anergy or weak, non-protective responses, further weakening adaptive antiviral immunity. In lymphoid tissues, loss of CD80/86 expression exacerbates germinal center dysfunction, delaying the generation of effective antibody production and contributing to the profound immunosuppression typical of acute CSF. By suppressing CD80/86 expression, CSFV disrupts a critical checkpoint in T-cell activation, thereby undermining antiviral immunity while promoting viral persistence and systemic dissemination. This co-stimulatory blockade is a key component of the virus’s broader immune-evasion strategy[5].

17. Nonclassical MHC exploitation as a viral immune-evasion strategy

CSFV, like other viruses, increasingly exploit nonclassical MHC molecules to evade immune detection and modulate host responses. Unlike classical MHC-I and MHC-II molecules, which are central to antigen presentation and T-cell activation, nonclassical MHC molecules (such as MHC-Ib family members) have restricted expression patterns, limited polymorphism, and specialized immunomodulatory functions[66]. Viruses manipulate these molecules to escape CTL killing, modulate natural killer (NK) cell activation, and shape a suppressive immune microenvironment. One key immune evasion strategy is the upregulation of inhibitory nonclassical MHC molecules, which mimic the host’s “self” signature to blunt NK cell-mediated cytotoxicity[67]. By creating a pseudo-healthy cellular phenotype, viruses hinder NK cell recognition of infected cells that would otherwise be targeted due to reduced classical MHC-I molecules. Simultaneously, viruses can downregulate activating nonclassical MHC ligands, limit NK cell activation, and facilitate persistence.

For CSFV, which already suppresses classical MHC-I and MHC-II pathways, this manipulation of nonclassical MHC molecules provides an additional layer of immune escape. The virus drives APCs toward tolerogenic states, where nonclassical MHC molecules gain functional dominance. These phenotypic shifts reduce T-cell responsiveness, impair co-stimulatory interactions, and support regulatory or anti-inflammatory signaling pathways that favor viral

survival[68,69]. Emerging evidence suggests that CSFV-induced cytokine environments (*e.g.*, elevated IL-10) further modulate nonclassical MHC expression, reinforcing immune suppression and dampening antiviral response. By specifically targeting nonclassical MHC molecules, CSFV and other viruses effectively bypass both innate and adaptive immune checkpoints. This subtle yet powerful mechanism of immune escape, complements suppression of classical MHC pathways, contributing to chronic infection and disease severity[2,3,15].

18. Organelle damage induced by CSFV

CSFV induces widespread organelle damage in infected cells, contributing significantly to viral replication efficiency, immune evasion, and cell death. Early during infection, CSFV remodels the endoplasmic reticulum (ER) to form replication-friendly membranous structures while simultaneously triggering ER stress. Prolonged ER stress activates the unfolded protein response, leading to dysregulated protein synthesis, impaired antigen processing, and, in severe cases, apoptosis[2,24,70]. CSFV also disrupts mitochondrial integrity, causing depolarization of the mitochondrial membrane and perturbing normal mitochondrial metabolic processes and antiviral signaling functions. By interfering with mitochondrial antiviral signaling protein and altering reactive oxygen species production, CSFV blunts type I IFN induction and weakens innate immune defences. Mitochondrial dysfunction further amplifies cell death pathways, contributing to lymphoid depletion and tissue damage, which are characteristics of acute CSF[71,72].

In addition, CSFV manipulates lysosomal and endolysosomal compartments, thereby impairing autophagic flux and antigen degradation pathways. Disrupted lysosomal function prevents efficient viral clearance and weakens MHC-II-mediated antigen presentation, further reinforcing CSFV’s immune-evasion strategies[2,34]. CSFV also induces alterations in Golgi structure and vesicular trafficking, which interfere with cytokine secretion and processing of membrane protein. Collectively, CSFV-induced damage to ER, mitochondria, lysosomes, and Golgi apparatus reshapes cellular homeostasis to favor viral replication while driving immunopathology and apoptosis. This organelle-targeted disruption is a central feature of CSFV pathogenesis and a key contributor to the profound immunosuppression observed during infection[24,73].

19. Implications for vaccine design

The extensive immune modulation exerted by CSFV, including disruption of antigen presentation, suppression of IFN signaling, impairment of macrophage and DC function, and induction of

lymphoid damage, highlights the need for next-generation vaccines that can overcome these immunoevasive strategies. Effective vaccine design must prioritize robust activation of innate immune responses, particularly targeting pathways that circumvent CSFV-mediated suppression of type I IFNs and NF- κ B signaling. Incorporating adjuvants or molecular patterns that strongly activate PRRs (e.g., TLR7/8, cGAS-STING) may help restore efficient antigen processing and facilitate T-cell priming. Given CSFV-driven targeted downregulation of MHC-I and MHC-II pathways, vaccine platforms should ensure high-quality antigen presentation[21,74]. Replication-deficient viral vectors, nanoparticle-based delivery systems, and mRNA vaccines can enhance endogenous antigen processing and co-stimulatory signaling, promoting eliciting stronger CD4⁺ and CD8⁺ T-cell responses. Strategies that preserve DC maturation and upregulate expression of CD80/86 would resolve a key bottleneck in T-cell activation[75].

CSFV-mediated suppression of humoral immunity and germinal center dysfunction underscores the importance of inducing potent, sustained neutralizing antibody responses. Stabilized E2 immunogens, multivalent antigen presentation, and prime-boost immunization regimens may help overcome delayed or weak seroconversion[76,77]. Finally, because CSFV skews macrophage and $\gamma\delta$ T-cell polarization toward regulatory or dysfunctional phenotypes, vaccines that promote balanced M1-like macrophage activation and timely IFN- γ production may enhance protective immunity. Overall, understanding CSFV immune evasion mechanisms provides a blueprint for vaccine design that enhances innate immune sensing, strengthens antigen presentation, boosts T-cell and B-cell effector functions, and counteracts viral immunosuppression, ultimately conferring more durable and broad-spectrum protective immunity.

20. Conclusion

CSFV employs a sophisticated array of immune-evasion strategies that collectively undermine host antiviral defences and drive severe disease outcomes. By targeting key components of the innate and adaptive immune systems, including IFN signaling, NF- κ B activation, antigen-presentation pathways, co-stimulatory molecule expression, and lymphoid integrity, CSFV transforms essential immune cells such as macrophages, DCs, B cells, and $\gamma\delta$ T cells into dysfunctional or immunopathogenic phenotypes. The virus's ability to suppress MHC-I and MHC-II pathways, modulate cytokine environments, and induce organelle damage further ensures efficient viral replication and systemic dissemination while hindering the development of protective immunity. These interconnected mechanisms highlight CSFV as a master immunomodulator and underscore the challenges in achieving robust and durable immune protection. A deeper understanding of how CSFV disrupts cellular

signaling cascade, antigen processing, and immune-cell interactions provides critical insights for design of next-generation vaccines and therapeutic interventions. Ultimately, targeting the molecular nodes exploited by CSFV while enhancing innate immune sensing and restoring functional antigen presentation offers a promising path toward improved control and eventual eradication of CSF.

Future research should focus on defining the precise molecular mechanisms by which CSFV disrupts MHC-I and MHC-II antigen presentation in macrophages and DCs. In particular, it is critical to elucidate how IFN suppression, NF- κ B modulation, and organelle stress converge to impair peptide processing and T-cell priming. A deeper understanding of macrophage polarization, DC tolerization, and $\gamma\delta$ T-cell dysfunction in the context of viral virulence will further clarify determinants of immune failure. Integrating single-cell sequencing and systems-level approaches may reveal immune heterogeneity influencing disease outcome. From a translational perspective, next-generation vaccines must be designed to overcome CSFV-driven suppression of antigen presentation and co-stimulatory signaling, while enhancing innate activation and restoring effective cellular and humoral immunity to achieve durable protection and improved disease control.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

NS was involved in conceptualization, data curation, formal analysis, and writing original draft. MV and MR were responsible for writing review and editing; KPS, JH, and SN contributed to

resources and software. SSP was responsible for conceptualization and supervision.

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