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Viral Infection of Macrophage Polarization in Porcine Alveolar Macrophages: Mechanisms and Therapeutic Interventions

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Abstract. The functional polarization of macrophages into pro-inflammatory M1 or anti-inflammatory M2 phenotypes is a critical battleground in host-virus interactions. This review systematically analyzes the mechanisms whereby porcine viruses (PRRSV, PCV2, and ASFV) subvert porcine alveolar macrophage (PAM) polarization to evade immunity and promote replication. It also details specific mechanisms such as receptor-mediated immune suppression (FcγR-ADE, Cap-gC1qR axis) and interferon pathway sabotage. A key finding is the critical distinction between true alveolar macrophages (PAMs) and pro-inflammatory pulmonary intravascular macrophages (PIMs), which are identified as the primary factories for PRRSV. Based on these mechanisms, it reveals novel therapeutic targets, including receptor blockade and polarization-modulating compounds like Toosendanin. This work not only refines the understanding of viral pathogenesis but also offers promising strategies against porcine viral diseases.

Keywords: Porcine alveolar macrophages (PAMs), Macrophage polarization, Viral immune escape, PRRSV, Therapeutic target

1. Introduction

Porcine alveolar macrophages (PAMs) are lung-resident professional phagocytes and antigen-presenting cells (APC) that play a pivotal role in regulation of inflammation and host defense. Their functional plasticity is best illustrated by the M1/M2 activation states, representing pro-inflammatory pathogen-killing versus anti-inflammatory tissue-protective phenotypes [1], which issummarised in Table 1.

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Table 1. M1 & M2 macrophage contrast [2-3]

Activated phenotype	M1	M2
Vitro exposure to	IFN-γ, LPS	IL-4, IL-10, IL-13
Effect	Triggers proinflammatory responses required to kill intracellular pathogens.	During inflammation, M2 macrophages serve to protect against tissue damage.
Expression markers	Pro-inflammatory cytokines IL-1β,IL-6,IL-12 ,TNF-α	Anti-inflammatory molecules IL-1 receptor antagonist (IL-1RA) and IL-10,Arg1

1.1. Macrophage polarization as a viral battleground

1.1.1. M1/M2 polarization in antiviral immunity and viral evasion strategies

Macrophages, key sentinels of innate immunity, exhibit remarkable plasticity by polarizing into distinct functional states in response to pathogens. During viral infection, the classical M1 phenotype plays a central role in initiating host defense, while the alternative M2 phenotype contributes to resolution and repair. However, viruses have evolved sophisticated strategies to manipulate this balance, subverting M1-driven immunity and exploiting M2-associated immunoregulation to enhance their survival and persistence [4].

1.1.2. M1-polarized macrophages: antiviral effectors

M1 macrophages are rapidly activated upon viral sensing through pattern recognition receptors (PRRs). They mount robust type I interferon responses, which establish an antiviral state in surrounding cells. In addition, they produce high levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-12) and reactive oxygen/nitrogen species that directly damage viruses and infected cells. Their enhanced phagocytosis and antigen presentation further bridge innate and adaptive immunity.

Despite their defensive role, macrophages can paradoxically serve as viral replication hubs. Many viruses exploit specific receptors (e.g., lectins, integrins) to enter macrophages and, once inside, establish productive infection that facilitates viral persistence and dissemination.

1.1.3. Viruses counteract M1 antiviral polarization

To ensure survival, viruses actively suppress the protective M1 phenotype through multiple strategies:

• Inhibition of PRR signaling: Viral proteins target upstream signaling molecules to block IFN-β induction.

• Disruption of IFN pathways: Many viruses inhibit JAK-STAT signaling downstream of interferon receptors, preventing ISG expression and dampening the antiviral state.

• Suppression of pro-inflammatory cytokines: Viral factors interfere with NF-κB activation or degrade cytokines/chemokines, reducing immune cell recruitment.

• Modulation of cell death pathways: By inhibiting apoptosis, viruses maintain a favorable environment for replication.

• Promotion of M2-like features: Some viruses induce immunosuppressive cytokines such as IL-10 and TGF-β, skewing macrophages toward an anti-inflammatory state even before full M2

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polarization.

1.2. Significance of Porcine Alveolar Macrophages (PAMs)

1.2.1. PRRSV

The key immunological mechanisms exploited by PRRSV to evade host defenses and promote infection are summarized in Table 2.

Table 2. Key immunological mechanisms of PRRSV

Mechanism	Effector molecules	Effect	Ref
Autophagy	LC3B ↑	Viral replication	[5]
Pro-inflammatory cytokine production	iRhom2/ADAM17/TNF-α axis↑	Lung damage	[6]
Enhanced anti-inflammatory signaling	IFN-α IFN-γ ↓(antiviral defense) TNF-α ↑(promote inflammation and induce fever and tissue injury) IL-10 ↑(associated with hindered viral clearance)	Immunosuppression	[7]

1.2.2. ASFV

ASFV infection enhances the phagocytic activity of PAMs by upregulating CD14 receptor expression, significantly increasing their ability to engulf bacteria (e.g.E.coli-EGFP) and apoptotic bodies (ApoBDs) [8]. This effect is mediated through the cGAS/STING/NF-κB pathway in infected cells and TLR9 pathway in uninfected bystander PAMs. This CD14-mediated mechanism represents a key strategy by which ASFV exploits PAM function, simultaneously amplifying viral spread and increasing host susceptibility to secondary infections

1.3. Research gaps and objectives

As mentioned above ASFV upregulates CD14 via the cGAS-STING-NF-κB axis, enhancing phagocytosis of apoptotic bodies (ApoBDs) and creating a positive feedback loop for viral transmission. Upon infection, viruses hijack cellular pathways to support their replication. Viruses also express proteins that are not incorporated into virions but are essential for the viral life cycle. In response, host cells activate defense mechanisms, including secretory pathways, to counter infection. However, viruses can subvert these same pathways to evade immunity [9]. Viruses depend on cellular machinery not only for entry, replication, transcription, assembly, and egress, but also for avoiding immune recognition. Importantly, the secretory activity of macrophages is tightly linked to their polarization states. Thus, understanding how viral infection reshapes macrophage secretion patterns is essential for elucidating the mechanisms that underlie viral manipulation of macrophage polarization.

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2. Viral mechanisms subverting macrophage polarization

2.1. Receptor-mediated immune suppression

2.1.1. FcγR-dependent ADE: a core immune suppression mechanism

PRRSV exploits antibody-dependent enhancement (PRRSV-ADE) through Fcγ receptors I and III (FcγRI/CD64, FcγRIII/CD16), which not only facilitates viral entry into porcine alveolar macrophages (PAMs) but also suppresses antiviral cytokine responses, particularly IFN-α and TNF-α [10]. Subneutralizing anti-PRRSV antibodies form immune complexes (ICs) with viral particles. These ICs bind FcγRI/III on PAMs and enhance viral entry by three to five foldx through clathrin-mediated endocytosis, as confirmed by chlorpromazine inhibition. At the same time, this interaction downregulates IFN-α and TNF-α production at both mRNA and protein levels within 24 hours post-infection, representing a dual mechanism of enhanced infection and immune suppression.

2.1.2. Signaling pathways underlying cytokine suppression

Two FcγR-mediated mechanisms account for cytokine suppression. One is inhibition of TLR signaling: IC binding to FcγRs disrupts TLR3/7/8 activation, reducing phosphorylation of downstream IRF3/7 and NF-κB, critical for IFN-α/TNF-α transcription. The other one is Amplification of IL-10 signaling: FcγR ligation triggers STAT3 phosphorylation, leading to sustained IL-10 upregulation (4–6 fold). IL-10 then inhibits NF-κB nuclear translocation, creating a feedback loop that further suppresses TNF-α/IFN-α.

2.1.3. Implications for PRRSV pathogenesis

By combining enhanced viral entry with cytokine suppression, FcγR-dependent ADE enables PRRSV to (1) Evade early innate immunity by suppressing IFN-α (key antiviral effector) and TNF-α (critical for macrophage activation) and (2) Establish persistent infection in PAMs—the primary viral target cells.

2.1.4. Therapeutic perspectives

The mechanistic insights from this study suggest potential strategies to counteract FcγR-dependent immune suppression: (1) Antibody engineering: Designing PRRSV antibodies with mutated Fc domains to avoid FcγR binding and (2) Receptor blockade: Developing FcγRI/III antagonists to prevent IC-mediated viral entry and immune suppression.

2.2. PCV2 Cap/gC1qR axis: disruption of M1 polarization and promotion of PRRSV coinfection

2.2.1. gC1qR-Cap interaction as a core suppression mechanism

The study identifies porcine gC1qR protein as the functional receptor for PCV2 capsid protein (Cap) [11]. Binding of Cap to gC1qR directly suppresses LPS/IFN-γ–induced M1 polarization in porcine macrophages, reducing TNF-α, IL-6, and iNOS expression by 60–80%. This impaired M1 polarization not only weakens macrophage antiviral activity but also synergistically favors PRRSV

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replication. In coinfection models, PCV2-infected macrophages fail to polarize toward M1 upon secondary PRRSV challenge, resulting in a 2.5-fold increase in PRRSV replication.

2.2.2. Signaling disruption via TLR4/NF-κB pathway

The Cap–gC1qR interaction interferes with key signaling events required for pro-inflammatory responses: (1) TLR4-MyD88 complex disruption: Cap binds gC1qR's C-terminal domain (aa 204–282), preventing TLR4 dimerization and MyD88 recruitment, thus inhibiting downstream NF-κB nuclear translocation and (2) Phosphoproteomics validation: Cap-gC1qR interaction reduces phosphorylation of IKKα/β (Ser176/180) and p65 (Ser536) by >70%, suppressing pro-inflammatory gene transcription.

2.2.3. Pathogenesis implications for coinfections

By paralyzing macrophage M1 polarization, PCV2 creates an immune-permissive environment that enhances PRRSV infection. In vivo, PCV2/PRRSV coinfection leads to a 3-fold increase in PRRSV load compared with single infection. Notably, serum soluble gC1qR levels correlate with coinfection severity, suggesting potential utility as a diagnostic marker and therapeutic target for controlling PCV2–PRRSV synergism.

2.3. Interferon pathway sabotage

2.3.1. TSN restores IRF1 to reprogram macrophage polarization and inhibit ASFV

ASFV suppresses IRF1 to dampen host immunity, but Toosendanin (TSN) restores IRF1 expression via JAK-STAT1 activation, thereby counteracting viral degradation and inhibiting replication [12]. Elevated IRF1 not only amplifies transcription of antiviral ISGs and reinstates IFN-γ responsiveness but also drives IRF1-dependent macrophage repolarization, as TSN-treated PAMs display increased $iNOS^+$ M1 cells and reduced $CD206^+$ M2 cells. Moreover, TSN acts synergistically with exogenous IFN-γ, with their combination markedly enhancing STAT1 phosphorylation and MHC-II expression, ultimately strengthening antigen presentation and T-cell activation.

2.3.2. IRF1 links IFN signaling and macrophage polarization

IRF1 is not only vital for IFN responses but also a master regulator of macrophage polarization. During pro-inflammatory (M1) polarization, IFN-γ activates JAK-STAT1 signaling, inducing IRF1 expression. IRF1 then drives transcription of M1 markers (e.g. iNOS, IL-12) and enhances antigen presentation via MHC-II. In ASFV-infected porcine alveolar macrophages (PAMs), however, a paradoxical polarization emerges: early upregulation of M2 markers (e.g.Arg-1, IL-10) is followed by sustained M1 signatures (e.g. TNF-α, IL-6). This "hybrid" state is attributed to IRF1 suppression, which dysregulates IFN-γ-driven M1 commitment while permitting transient immunosuppressive M2 skewing.

2.3.3. PRRSV-driven M2 bias: sustains viral persistence

As shown in Table 1, PRRSV infection itself skewed PAMs toward an M2 phenotype, creating a favorable microenvironment for viral persistence [13]. Triggering receptor expressed on myeloid cells 2 (TREM2) is an anti-inflammatory receptor that negatively regulates innate immunity,

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primarily expressed on porcine reproductive and respiratory syndrome virus (PRRSV) target cells (dendritic cells and macrophages). During PRRSV infection of PAMs in vitro, TREM2 expression increases; silencing TREM2 suppresses viral replication, whereas its overexpression enhances it. TREM2 modulates the virus-triggered inflammatory response, as knockdown potentiates early transcription of proinflammatory cytokines and type I interferons [14], with protein levels of IL-1β, IL-4, IL-10, and TNF-α significantly elevated in TREM2-silenced PAMs. These findings indicate that PRRSV drives M2 polarization, with CD163 serving as a key factor for viral entry and infection initiation.

3. Identity crisis: PAMs vs. Pulmonary Intravascular Macrophages (PIMs)

3.1. Redefining the target cell

Pulmonary intravascular macrophages (PIMs) act as primary PRRSV factories, producing high viral titers (>10^8 $TCID_{50}$/mL) and exhibiting a pro-inflammatory phenotype [15], whereas true PAMs are alveolar-resident, anti-inflammatory, and show low viral permissiveness. This study delivers a paradigm-shifting revelation in PRRSV infection. Traditionally isolated "porcine alveolar macrophages (PAMs)" are substantially contaminated by pulmonary intravascular macrophages (PIMs) [15]. Through rigorous phenotypic validation, including expression of CD163 and MHC-II, PIMs are identified as intravascular sentinels embedded in lung capillaries, distinct from alveolar-resident PAMs. These findings refine the understanding of PRRSV pathogenesis: PIMs functions as the dominant viral factories, producing exceptionally high infectious viral titers (>10^8 $TCID_{50}$/mL). This represents a greater than 10-fold increase compared to the PAMs produced. In vivo, PIM infection strongly correlates with viremia and lung viral load, confirming their role in systemic virus dissemination. Furthermore, PIMs drive pro-inflammatory pathology during PRRSV infection. Upon infection, PIMs significantly upregulate TNF-α and elevate IL-6/IL-8, directly fueling pulmonary inflammation. In contrast, PAMs exhibit minimal cytokine responses, underscoring PIMs as primary effectors of immunopathology. Therefore, future research must rigorously discriminate between these macrophage subsets. This distinction is essential to develop PIM-targeted antivirals and anti-inflammatories. It is also necessary to re-evaluate vaccine efficacy metrics, like controlling viremia may require PIM-focused strategies.

3.2. Implications for disease models — immortalized "PAM" lines (CD163) mimic PIMs

Primary PAMs present limitations for PRRSV studies due to their short lifespan, donor variability, and technical culture challenges [16], with rapid degradation of CD163 — a key receptor for PRRSV entry and inflammation modulation — being a critical issue [17]. To overcome these problems and enable standardized research, researchers develop immortalized macrophage line using ways like SV40 T-antigen transformation. This line maintains stable CD163 expression, enabling consistent PRRSV replication studies [18]. The engineered CD163-expressing immortalized line functionally mimic PIMs. Studies confirm their high permissiveness to PRRSV, demonstrating viral replication fidelity compares to primary PAMs, including the viral RNA synthesis and infectious virion yield. Furthermore, the $CD163^+$ immortalized cells secrete pro-inflammatory cytokines like TNF-α, IL-1β, and IL-8, which causes primary cell cytokine storms.

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3.3. Unified immortalized platforms for pathogenesis & therapy

Immortalized CD163^{+} macrophage lines eliminate inter-donor variability, enabling cross-lab reproducibility (shown in Table 3). These standardized models support reliable antiviral drug and vaccine candidate assessment [16, 18]. Critically, these platforms allow isolation of PRRSV-entry mechanisms from confounding immune variables, supporting mechanistic studies and therapeutic development.

Table 3. CD163 functions, therapeutic potential, and suitability in PAMs

CD163 and inflammation Theroy	Application in PAMs models	Resolved primary cell defects
CD163-mediated viral endocytosis	Enables high-fidelity PRRSV replication	Unstable CD163 in primary PAMs
CD163-HO-1 anti-inflammatory axis	Model replicates TNF-α/IL-10 balance post-infection	Short-term culture fails to maintain signaling
sCD163 as inflammation biomarker	Immortalized lines allow dynamic sCD163 shedding monitoring	Non-standardized sCD163 release in primary cells
Therapeutic potential of CD163 blockade	Used for receptor antagonist screening	Primary cells unfit for high-throughput drug tests

4. Translational strategies: from mechanisms to therapies

4.1. Blocking pathogenic receptor interactions

4.1.1. Mechanism: FcγR-mediated ADE exacerbates PRRSV pathogenesis

Understanding virus infection via the antibody-dependent enhancement (ADE) pathway is crucial for developing effective interventions against PRRSV. Specific activation of FcγRI or FcγRIII in PAMs during PRRSV infection not only significantly decreased the production of IFN-α and TNF-α, but also significantly increased the production of IL-10 and significantly facilitated PRRSV replication [10]. Enhanced infection and replication of PRRSV in the presence of the antibody specific for the virus has been demonstrated in vivo and in vitro, a phenomenon known as antibody-dependent enhancement (ADE) that promotes the attachment and internalization of the virus into its host cells by Fc receptor-mediated endocytosis. As shown in Table 4, subneutralizing anti-PRRSV antibodies bind viral envelope proteins, forming immune complexes (ICs). ICs engage FcγRI (CD64) and FcγRIII (CD16) on porcine alveolar macrophages (PAMs), enhancing viral entry via clathrin-mediated endocytosis.

Table 4. Therapeutic strategies targeting FcγR to prevent ADE

Approach	Molecular target	Therapeutic effect
Anti-FcγR Agents	FcγRI/III (CD64/CD16)	Block IC binding, abolishing ADE-enhanced infection
Fc-Engineered Antibodies	Fc domain of IgG (knockdown FcγRI or FcγRIII)	Reduce FcγR affinity, prevent ADE in vivo
Soluble Decoy Receptors	Recombinant FcγRIIb ectodomain	Compete with FcγRI/III for IC binding

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4.1.2. Mechanism: PCV2 capsid-gC1qR interaction suppresses M1 polarization

PCV2 actively inhibits M1 macrophage polarization and associated gene expression in PAMs both ex vivo and in vitro. The inhibition of M1 polarization induced by other pathogens depends on the viral Cap protein and host gC1qR protein, which modulate JAK/STAT signaling [11]. The mechanism involves PCV2 Cap binding directly to gC1qR on the surface of porcine marcrophages. This specific interaction sabotages the macrophage's inflammatory response by blocking M1 polarization normally triggered by TLR ligands or IFN-γ stimulation. Consequently, key M1 markers like iNOS, TNF-α and IL-12 show significantly reduced expression.

In PRRSV and PCV2 coinfection, Cap-gC1qR disrupts STAT1 phosphorylation and IRF3 nuclear translocation, suppressing antiviral responses. Targeting this Cap-gC1qR interaction presents a promising therapeutic strategy for coinfections. One approach focuses on developing specific biologic antagonists designed to block gC1qR, thereby restoring M1 functionality specifically in PRRSV/PCV2 coinfected hosts. Alternatively, researchers propose designing Cap-mimetic peptides. These synthetic peptides would competitively bind to gC1qR, preventing the authentic viral Cap protein from engaging its receptor and disrupting macrophage function.

4.2. Polarization-targeted compounds — TSN

Toosendanin (TSN), a bioactive compound from traditional medicine, suppresses African swine fever virus (ASFV) replication by targeting the immunophenotypic polarization of macrophages [12]. Using PAMs as a model, TSN was found to significantly upregulate IRF1, thereby enhancing the IFN-I pathway and ultimately inhibiting ASFV proliferation. TSN-driven immune reprogramming centered on IRF1activation. By promoting IRF1 expression, TSN shifts macrophages to an antiviral M1-like phenotype. Elevated IRF1 directly enhances IFN-β production, establishing a positive feedback loop that bolsters innate immunity. Consequently, M1-polarized macrophages exhibit increased proinflammatory cytokines (TNF-α, IL-6) and antiviral genes. TSN-induced IRF1/IFN activation creates a host microenvironment restrictive to viral replication, establishing TSN as a promising polarization-targeted compound and offering a novel paradigm for antiviral immunotherapy.

5. Conclusion and future directions

PRRSV, PCV2, and ASFV manipulate porcine alveolar macrophage (PAM) polarization to evade immunity. PRRSV induces an M2-biased state via FcγR-mediated AED. PCV2 inhibits M1 through Cap-gC1qR interaction. ASFV degrades IRF1 to suppress antiviral responses. TSN restores the JAK-STAT1-IRF1 axis to promote M1 repolarization. Conventional “PAMs” are pro-inflammatory PIMs with high viral titers, explaining PRRSV pathogenesis.

Immortalized $CD163^{+}$ lines address practical challenges but may not reflect the in vivo environment. Current methods lack real-time tracking of polarization switches. Synergistic mechanisms in PCV2–PRRSV coinfections remain unclear. Future work should employ in vivo and organoid models, advanced live-cell imaging, and high-throughput screening for gC1qR antagonists. Optimizing TSN-derived therapeutics and targeting macrophage polarization plasticity offers promising antiviral strategies.

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