Review

FcγR–ACE2 Cooperative Antibody-Dependent Enhancement in Human and Veterinary Coronaviruses: Mechanisms, Comparative Immunopathology, and Therapeutic Implications

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Review

FcγR–ACE2 Cooperative Antibody-Dependent Enhancement in Human and Veterinary Coronaviruses: Mechanistic Insights, Comparative Immunology, and Implications for Nano-Engineered Immunomodulatory Platforms

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Abstract

Antibody-dependent enhancement (ADE) is a paradoxical immunological phenomenon in which pre-existing antibodies facilitate viral entry into host cells rather than conferring protection. ADE has been extensively characterised in flaviviral systems, most notably dengue virus (DENV), and presents a significant challenge for vaccine development and antibody-based therapeutic design. In coronavirus infections, ADE operates through both classical Fc gamma receptor (FcγR)-mediated pathways and an intrinsic signalling mechanism involving inhibitory FcγRIIb-mediated suppression of the type I interferon (IFN-I) response. Of critical translational relevance is the proposed cooperative FcγR–angiotensin-converting enzyme 2 (ACE2) entry model for SARS-CoV-2, wherein virus–antibody immune complexes simultaneously engage ACE2 through the viral spike receptor-binding domain (RBD) and FcγRIIa through the antibody Fc region on the same macrophage surface. This cooperative dual-receptor engagement may stabilise virion attachment, augment endosomal uptake, and trigger downstream signalling cascades that suppress antiviral immunity, potentially contributing to severe COVID-19 immunopathology. Feline infectious peritonitis virus (FIPV) represents one of the most rigorously documented biological systems in which antibody-mediated macrophage infection directly determines systemic disease outcome, providing a critical comparative framework for understanding coronavirus ADE across species. This comprehensive review integrates current knowledge of FcγR biology, coronavirus cell entry mechanisms, intracellular signalling cascades, cytokine dysregulation, comparative veterinary immunopathology, and nano-engineered immunomodulatory platforms for ADE-safe vaccine development. We critically evaluate lipid nanoparticle mRNA vaccines, virus-like particles, and polymeric nanoparticle systems as rational strategies to elicit selective neutralising antibody responses while mitigating ADE risk. We also highlight key unresolved mechanistic questions and future research directions essential for the development of safer vaccines and therapeutics against both current and emerging coronaviruses in human and veterinary medicine.

Keywords: antibody-dependent enhancement; Fc gamma receptor; ACE2; SARS-CoV-2; FIPV; coronavirus immunopathology; lipid nanoparticle; virus-like particle; PLGA; intrinsic ADE; cytokine storm; veterinary immunology; nanomedicine

1. Introduction

The global emergence of SARS-CoV-2 and the COVID-19 pandemic renewed scientific scrutiny of antibody-dependent enhancement (ADE), a process in which virus-specific antibodies paradoxically facilitate rather than prevent cellular infection. ADE was first described in relation to

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dengue virus (DENV) in the 1960s and has since been documented in HIV, Zika, Ebola, West Nile, and multiple coronaviruses. The classical ADE model involves Fc gamma receptor (FcγR)-mediated endocytosis of IgG-opsonised virions into immune cells, bypassing or augmenting normal entry routes. A second pathway — intrinsic ADE — operates via inhibitory FcγRIIb signalling, suppressing antiviral interferon production without necessarily altering viral tropism.

The mechanistic complexity of ADE in coronaviruses is compounded by the unique biology of these pathogens. Unlike flaviviruses, coronaviruses primarily infect epithelial cells through spike glycoprotein interaction with specific host receptors: ACE2 for SARS-CoV-2 and SARS-CoV-1; aminopeptidase N (APN/CD13) for HCoV-229E and feline coronavirus; and DPP4 for MERS-CoV. Coronavirus cellular tropism overlaps only partially with FcγR-expressing myeloid cells, yet emerging data confirm that macrophages and monocytes co-expressing ACE2 and FcγRIIa can be productively infected through ADE-facilitated pathways.

SARS-CoV-2 has provided an unprecedented opportunity to study ADE in a human coronavirus pandemic pathogen. In vitro and animal model data suggest that anti-spike antibodies at sub-neutralising concentrations or against antigenically drifted variants may engage FcγRs on myeloid cells, with the potential for cooperative interaction with ACE2 on the same cell surface. The interaction between FcγR and ACE2 pathways — individually well-characterised but jointly under-explored — defines a mechanistically distinct entry mode that may amplify replication and inflammatory signalling in macrophages, contributing to cytokine release syndrome in severe COVID-19.

Veterinary medicine provides powerful and ethically accessible comparative models for coronavirus ADE. Feline infectious peritonitis virus (FIPV), a mutant of feline enteric coronavirus (FCoV), causes a uniformly fatal systemic granulomatous disease in domestic cats in which ADE via FcγR-mediated macrophage infection is central, well-characterised, and immunologically instructive. The FIPV field documented antibody-enhanced disease following vaccination before the field of human coronavirus vaccinology faced analogous challenges — providing critical translational lessons that remain directly applicable to SARS-CoV-2 vaccine safety evaluation.

Nanotechnology has emerged as a transformative platform for addressing ADE-related challenges in vaccine development. Lipid nanoparticle (LNP) mRNA vaccines, virus-like particle (VLP) systems, and biodegradable polymeric nanoparticles enable unprecedented control over antigen presentation geometry, epitope density, and immunological context, with demonstrated capacity to selectively promote neutralising antibody (nAb) induction while minimising non-neutralising antibody responses that carry ADE risk.

This review provides a comprehensive synthesis of coronavirus ADE mechanisms, comparative immunopathology, and nano-engineered countermeasure strategies, organised to serve as both a mechanistic reference and translational guide for researchers working at the intersection of virology, immunology, and nanomedicine.

2. Molecular Basis of Antibody-Dependent Enhancement

2.1. Classical Extrinsic ADE: FcγR-Mediated Viral Entry

Classical extrinsic ADE involves the direct facilitation of viral entry into immune cells via Fc receptor-mediated internalisation of antibody-opsonised virions. IgG antibodies comprise antigen-binding Fab fragments and a constant Fc region; while the Fab binds viral surface antigens, the Fc region engages FcγRs on immune cells. When viral neutralisation is incomplete — as occurs at sub-neutralising antibody concentrations, with low-affinity antibodies, or against heterologous antigenic variants — virus–antibody immune complexes form that display functional viral surface proteins alongside accessible Fc regions. FcγR clustering upon immune complex binding triggers clathrin-mediated endocytosis, delivering replication-competent virions to intracellular compartments where productive infection can be established.

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Figure 1. *Two mechanistic pathways of antibody-dependent enhancement (ADE) in coronavirus infections. Panel A (Classical/Extrinsic ADE): Sub-neutralising IgG opsonises the virion, enabling FcγRIIa-mediated endocytosis into macrophages/monocytes and enhanced viral replication. Panel B (Intrinsic ADE): Inhibitory FcγRIIb engagement activates ITIM/SHP-1–2/SOCS1–3 signalling, silencing the IFN-I antiviral response and enabling immune evasion without necessarily altering cellular tropism.*

2.2. Intrinsic ADE: FcγRIIb-Mediated IFN-I Suppression

Beyond classical extrinsic ADE, coronaviruses exploit an intrinsic ADE pathway mediated specifically through the inhibitory receptor FcγRIIb (CD32b). Unlike activating FcγRs that signal via ITAMs, FcγRIIb signals through an immunoreceptor tyrosine-based inhibitory motif (ITIM), recruiting phosphatases SHP-1 and SHP-2 upon Tyr-phosphorylation. Engagement of FcγRIIb by IgG-opsonised SARS-CoV-2 activates this inhibitory axis, which converges on the JAK-STAT pathway to suppress IFN-I production via induction of SOCS1 and SOCS3. IFN-α and IFN-β normally induce antiviral interferon-stimulated genes (ISGs) that restrict replication, enhance antigen presentation, and recruit adaptive immunity. Blunting this response through intrinsic ADE provides SARS-CoV-2 with a critical temporal window for unchecked replication before adaptive immunity is mobilised.

Critically, intrinsic ADE can operate independently of altered viral entry route — the IFN-I suppression mediated by FcγRIIb signalling affects the entire antiviral transcriptional programme regardless of whether viral entry occurs via ACE2 or FcγR. This distinguishes intrinsic ADE mechanistically from classical ADE and means that even conventional ACE2-mediated infection may be immunologically exacerbated by concurrent FcγRIIb signalling on adjacent infected macrophages.

2.3. Antibody Glycosylation and ADE Risk

The glycosylation state of the IgG Fc region at Asn297 profoundly influences FcγR affinity and ADE risk. Afucosylated IgG1 — which lacks core fucose on the Fc N-glycan — exhibits dramatically enhanced binding to FcγRIIIa, increasing ADCC and ADE potential. Elevated afucosylated anti-spike IgG levels have been reported in severe COVID-19 patients following natural SARS-CoV-2 infection

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but are notably absent following mRNA vaccination. This differential glycosylation profile between infection-induced and vaccine-induced antibodies may partly explain why ADE has not been observed clinically in mRNA-vaccinated populations, and underscores the importance of Fc glycoengineering in vaccine and therapeutic antibody design.

3. Fc Gamma Receptor Biology in Immune Cells

3.1. Classification, Structure, and Expression

Fc gamma receptors constitute a family of immunoglobulin superfamily members encoded on chromosome 1q23, comprising six distinct proteins: FcγRI (CD64), FcγRIIa (CD32a), FcγRIIb (CD32b), FcγRIIc (CD32c), FcγRIIIa (CD16a), and FcγRIIIb (CD16b). These are classified into activating receptors (FcγRI, FcγRIIa, FcγRIIc, FcγRIIIa, FcγRIIIb) and a single inhibitory receptor (FcγRIIb). The extracellular domains consist of one (FcγRII, FcγRIII) or two (FcγRI) immunoglobulin-like C2-type domains interacting with the IgG Fc CH2 region, with binding affinities ranging from ~10^{-9} M for FcγRI to ~10^{-5} M for FcγRIIIb.

Table 1. Classification and Properties of Human Fc Gamma Receptors Relevant to ADE.

FcγR Type	CD Name	IgG Affinity	Cell Expression	Signal Motif	ADE Relevance
FcγRI	CD64	High (Kd ~10^{-9} M)	Monocytes, Macrophages, DCs	ITAM (γ-chain)	Primary mediator; binds monomeric IgG; high-avidity ADE
FcγRIIa	CD32a	Intermediate	Macrophages, Neutrophils, Platelets	ITAM (intrinsic)	Activating; central coronavirus ADE receptor; H131 polymorphism
FcγRIIb	CD32b	Intermediate	B cells, Macrophages, DCs	ITIM (inhibitory)	Intrinsic ADE; IFN-I suppression via SHP-1/2; SOCS induction
FcγRIIIa	CD16a	Low–Intermediate	NK cells, Macrophages, Monocytes	ITAM (γ/ζ-chain)	ADCC; ADE in monocytes; V158 polymorphism affects affinity
FcγRIIIb	CD16b	Low	Neutrophils only	GPI-linked (no signalling)	Phagocytosis; minimal direct ADE role

Table 1. Classification of human FcγR family members. ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; DCs, dendritic cells.

3.2. Intracellular Signalling Cascades in ADE

Activating FcγR signalling in macrophages proceeds through Src-family kinase (Lyn, Fyn) phosphorylation of ITAM tyrosines, generating docking sites for Syk kinase. Syk activates PLCγ → IP3/DAG, mobilising intracellular calcium and PKC. Parallel PI3K → PIP3 → Akt/mTOR activation, together with NF-κB and ERK/MAPK transcriptional activation, produces cytokine secretion and phagocytosis. In ADE, this cascade is co-opted by internalised virions to create a permissive intracellular environment. The downstream result is IL-6, IL-10, TNF-α overproduction with IFN-I suppression via SOCS induction — the cytokine signature of severe COVID-19.

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Figure 5. *Intracellular signalling cascade downstream of FcγRIIa engagement during ADE. Syk kinase and PI3K activation diverge into multiple pro-inflammatory and immunosuppressive pathways, culminating in IL-10/IL-6 production, SOCS1/3-mediated IFN-I silencing, and TNF-α/IL-1β release — collectively generating a pro-viral, cytokine-dysregulated macrophage environment characteristic of ADE-mediated coronavirus immunopathology.*

3.3. FcγR Polymorphisms and Individual ADE Susceptibility

The FcγRIIa-H131R polymorphism significantly influences ADE susceptibility: H131 homozygotes exhibit higher binding affinity for IgG2/IgG3 immune complexes, predisposing to more efficient FcγR-mediated viral uptake. This polymorphism has been associated with differential dengue haemorrhagic fever susceptibility and is hypothesised to influence macrophage ADE risk in SARS-CoV-2 infection. Similarly, the FcγRIIIa-V158F polymorphism influences NK-cell ADCC and macrophage activation. Population-level differences in FcγR polymorphism frequencies may partially explain heterogeneity in COVID-19 severity independent of comorbidities, and FcγR genotyping may have future value in identifying individuals at highest risk of ADE-mediated immunopathology.

4. Coronavirus Cell Entry Mechanisms

4.1. Spike Glycoprotein Architecture and RBD–ACE2 Interaction

The coronavirus spike (S) glycoprotein is a class I fusion protein existing as a homotrimer on the viral envelope. S1 contains the receptor-binding domain (RBD) and N-terminal domain (NTD); S2 mediates membrane fusion. SARS-CoV-2 RBD engages ACE2 through a buried surface area of ~864 Å², involving key contact residues Lys417, Leu452, Tyr453, Gln493, Ser494, Asn501, and Tyr505 on the RBD. A multibasic furin cleavage site (PRRAR↓S) at the S1/S2 boundary — absent in SARS-CoV-

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1 — enables pre-activation of virions during biogenesis, significantly enhancing transmissibility and facilitating direct TMPRSS2-mediated fusion at the plasma membrane.

4.2. Dual Entry Routes: TMPRSS2-Mediated Fusion vs Endosomal Cathepsin Pathway

SARS-CoV-2 employs two principal entry routes: (1) plasma membrane fusion dependent on TMPRSS2 (direct cytoplasmic genome delivery, minimal endosomal TLR exposure), and (2) endosomal entry via cathepsins B/L following clathrin-mediated endocytosis. The balance between these routes varies by cell type and is critically altered in ADE scenarios where FcγR-mediated endocytosis — initiated by immune complex uptake — directs virions into the endosomal compartment regardless of TMPRSS2 availability. This redirection potentially alters innate immune sensing (endosomal TLR7 activation) and fusion efficiency, with consequences for both viral replication and inflammatory signalling.

5. The Cooperative FcγR–ACE2 Entry Model

5.1. Rationale, Structural Feasibility, and Experimental Evidence

The cooperative FcγR–ACE2 entry model proposes that SARS-CoV-2–antibody immune complexes may simultaneously engage ACE2 (via viral RBD) and FcγRIIa (via antibody Fc) on the same immune cell surface. Both receptors are co-expressed on human macrophages and monocytes. IgG antibodies (~14 nm) binding the RBD position their Fc ~15–20 nm from the viral membrane — geometrically compatible with simultaneous FcγR engagement on an opposing cell membrane stabilised by ACE2 anchoring. Cryo-electron tomographic dimensional analysis of SARS-CoV-2 spikes (inter-trimer spacing 15–25 nm) confirms the structural feasibility of this ternary complex.

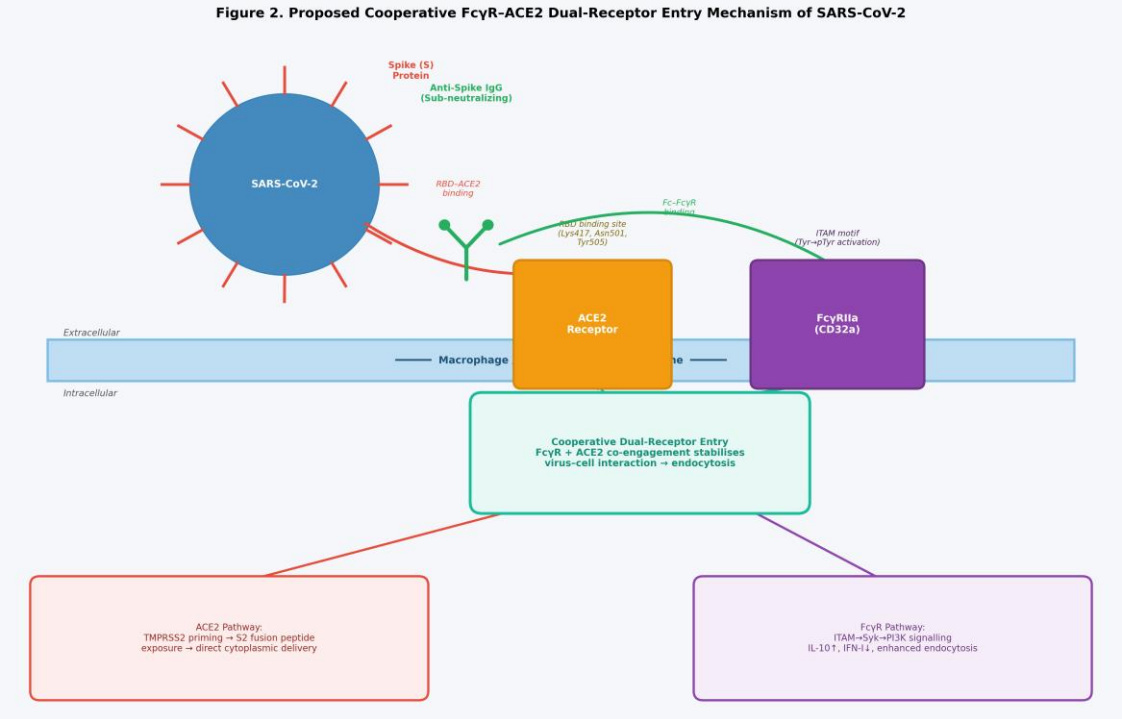

Figure 2. *Proposed cooperative FcγR–ACE2 dual-receptor entry mechanism of SARS-CoV-2 in macrophages/monocytes. The SARS-CoV-2 virion (displaying spike protein with RBD in "up" conformation) simultaneously engages ACE2 via RBD and FcγRIIa via anti-spike IgG Fc. Cooperative dual-receptor engagement stabilises virus–cell contact and enhances endocytosis. Downstream ACE2 (TMPRSS2 activation) and FcγR (ITAM→Syk→PI3K→NF-κB) signals converge, producing IL-10 upregulation and IFN-I suppression that create an intracellular environment permissive for viral replication.*

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Experimental support for this model includes: (i) Liu et al. (2019) and subsequent confirmatory studies demonstrating sub-neutralising anti-RBD antibodies facilitate SARS-CoV-2 infection of FcγRIIa-expressing macrophages, abolished by FcγR blockade but not ACE2 inhibition alone; (ii) Zhao et al. (2020) demonstrating IgG-triggered macrophage IL-6/TNF-α production in rhesus macaques, exacerbating lung pathology independently of direct viral replication enhancement; and (iii) population data correlating elevated non-neutralising anti-NTD/S2 IgG with severe COVID-19.

5.2. Implications for Antibody-Based Therapeutics

The cooperative entry model has direct implications for therapeutic monoclonal antibody (mAb) design. Any anti-spike IgG administered at concentrations transiently below its neutralisation EC50 — during pharmacokinetic clearance or upon variant-mediated neutralisation resistance — carries theoretical ADE risk through its intact Fc region. LALA, LALAPG, and YTE Fc mutations introduced into several therapeutic coronavirus mAbs abrogate activating FcγR binding while preserving Fab functionality, addressing the classical ADE pathway. Engineering strategies that selectively eliminate FcγRIIa binding while modulating FcγRIIb engagement represent a precision approach to ADE-safe therapeutic antibody development.

6. Intracellular Trafficking and Viral Fate After FcγR-Mediated Entry

Following FcγR-mediated endocytosis, virus-containing phagosomes undergo progressive acidification through early endosomes (EEA1+, Rab5+) to late endosomes (LAMP-1+, Rab7+). In canonical phagocytic processing, lysosomal fusion delivers cargo to a degradative environment (pH 4.5–5.0). However, coronaviruses exploit the low-pH late endosomal environment for cathepsin L-mediated spike activation, enabling membrane fusion and genome cytoplasmic delivery from within endosomes. The key mechanistic question is whether FcγR-internalised coronaviruses are more efficiently delivered to cathepsin-permissive late endosomes compared to ACE2-mediated entry, and whether ITAM signalling modulates endosomal maturation kinetics.

Within macrophages infected via ADE, SARS-CoV-2 replication proceeds through the replication-transcription complex (RTC) producing genomic RNA copies and sub-genomic mRNAs. Importantly, macrophage-infected coronaviruses frequently undergo abortive or semi-abortive replication — sufficient for viral RNA synthesis and protein production but without generating abundant infectious progeny. This abortive phenotype may trigger dysregulated cytokine production (via pattern recognition of double-stranded RNA replication intermediates) without productive viral amplification, contributing to the inflammatory but not necessarily viremic component of ADE pathology.

SARS-CoV-2 encodes at least 16 non-structural proteins (nsp1–16) and multiple accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8, N) that antagonise IFN-I production at multiple points: cytoplasmic RNA sensing (RIG-I/MDA5 inhibition via nsp3-PLpro), STING-TBK1-IRF3 signalling (nsp13 ATPase), STAT1/2 nuclear translocation (ORF6), and ISG expression (nsp1 ribosome stalling). Combined with FcγRIIb-SOCS-mediated extrinsic IFN-I suppression, these mechanisms synergise to create a profoundly immunosuppressive intracellular environment highly permissive for viral replication.

7. Veterinary Coronavirus ADE: The FIPV Paradigm

7.1. FCoV Biology and the Enteric-to-FIPV Conversion

Feline coronavirus (FCoV) is a prevalent enteric pathogen of domestic and wild felids, with seroprevalence reaching 90% in multi-cat environments. Two biotypes are recognised: feline enteric coronavirus (FECV), which causes mild to moderate enteritis, and feline infectious peritonitis virus (FIPV), the causative agent of the uniformly fatal systemic disease FIP. The FECV-to-FIPV transition arises through spontaneous mutations in the viral genome during persistent enteric replication,

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primarily in the spike S gene (altered receptor usage: APN to FcγR macrophage tropism) and the 3c gene (functional truncation correlating strongly with FIPV phenotype emergence). This endogenous mutational pathway means that FIPV cannot be eliminated through biosecurity or vaccination of the source FCoV, since each FIPV case arises de novo in an individual host.

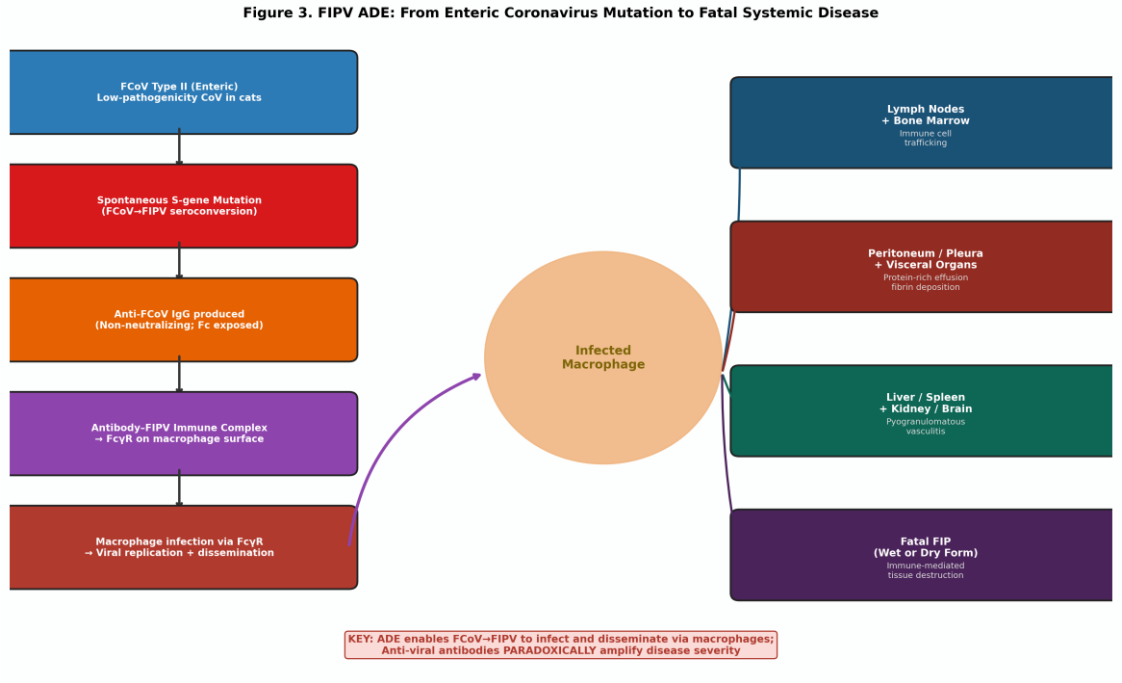

Figure 3. *FIPV ADE pathogenesis: from enteric FCoV mutation to fatal systemic disease. Following FCoV→FIPV spike mutation, non-neutralising anti-FCoV IgG opsonises FIPV, forming immune complexes that are internalised by peritoneal and pleural macrophages via FcγR. Infected macrophages disseminate virus systemically to lymph nodes, liver, spleen, kidney, and CNS, producing pyogranulomatous vasculitis and protein-rich effusions characteristic of fatal wet or dry FIP. ADE is the obligate amplification mechanism enabling this lethal systemic spread.*

7.2. FcγR-Mediated Macrophage Infection: Core ADE Mechanism

The hallmark virological feature distinguishing FIPV from FECV is pronounced macrophage tropism. Olsen et al. and Vennema et al. established that primary peritoneal macrophages are not permissively infected by FIPV in the absence of antibodies, but infection is dramatically enhanced in antibody-seropositive animals or upon addition of anti-FCoV serum. FcγR blockade with anti-FcγR antibodies completely abrogates this enhancement, confirming FcγR as the obligate entry mediator under ADE conditions. Within the macrophage, FIPV replicates productively, generating progeny virions that infect additional macrophages and disseminate via the lymphovascular system to peritoneum, pleura, liver, spleen, kidney, and brain — producing the pyogranulomatous vasculitis and effusions characteristic of fatal FIP.

7.3. Vaccine-Enhanced Disease in FIPV: Translational Lessons

Vaccination studies with early FIPV vaccines — including whole inactivated FIPV, recombinant spike protein, and attenuated strains — paradoxically accelerated disease in vaccinated animals upon challenge in a phenomenon termed "early death syndrome" (antibody-mediated enhancement of FIPV infection, AMEFI). Vaccinated cats with non-neutralising anti-spike IgG developed faster, more severe FIP than unvaccinated controls, as opsonising antibodies enabled enhanced macrophage uptake of challenge virus. This directly underscores the critical principle applicable to SARS-CoV-2 vaccine design: a vaccine must induce fully neutralising antibody titres above a protective threshold; sub-threshold antibody responses may be worse than no humoral response.

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The approved intranasal FIPV vaccine (Primucell-FIP, Zoetis) based on a temperature-sensitive DF2 strain achieves protection through mucosal IgA and T cell responses with minimal systemic IgG that could mediate ADE — a strategy with direct parallels to intranasal coronavirus vaccine development. The recent clinical success of GS-441524 (the remdesivir parent compound) in treating FIP with >80% remission rates provides proof-of-concept that targeting the viral RdRp is effective against both FIPV and SARS-CoV-2, validating this therapeutic target across alphacoronavirus and betacoronavirus systems.

Table 3. Comparative Analysis of ADE in SARS-CoV-2 vs FIPV.

Parameter	SARS-CoV-2 (Human)	FIPV (Feline)
Coronavirus lineage	Betacoronavirus (lineage B)	Alphacoronavirus (FCoV type I/II)
Primary entry receptor	ACE2 (+ TMPRSS2 co-factor)	APN/CD13; FcγR in ADE
ADE mechanism	Extrinsic (FcγRIIa + ACE2 cooperative) + Intrinsic (FcγRIIb-SOCS)	Classical FcγR-mediated macrophage entry; antibody accelerates entry
Primary ADE target cell	Alveolar macrophages, monocytes	Peritoneal/pleural macrophages (tissue-resident)
Key pathogenic cytokines	IL-6, IL-10, TNF-α; IFN-I suppressed	IL-6, TNF-α, IL-1β; IL-12 reduced
Tissue pathology	Diffuse alveolar damage, ARDS	Pyogranulomatous vasculitis, exudative effusions
Mortality in severe cases	~15–40% (critically ill); overall ~1–3%	Near 100% without antiviral therapy
Vaccine-enhanced disease	Not observed with mRNA vaccines; theoretical risk exists	Documented with whole-virus and recombinant spike vaccines
Therapeutic antiviral	Remdesivir, Paxlovid, molnupiravir	GS-441524 (remdesivir parent compound)
Gold-standard ADE model?	Human — limited by ethical constraints on controlled challenge	YES — natural cat model; controlled challenge studies possible

Table 3. Direct comparison of ADE-relevant parameters between SARS-CoV-2 and FIPV. FIPV provides the most complete natural coronavirus ADE model, with nearly 100% fatal outcome, directly demonstrable antibody-mediated macrophage entry, and documented vaccine-enhanced disease — all directly translatable to coronavirus vaccine safety evaluation.

8. Nano-Engineered Immunomodulatory Platforms for ADE-Safe Vaccination

8.1. Antigen Engineering Principles to Minimise ADE Risk

The central immunological challenge for ADE-safe coronavirus vaccines is selectively eliciting antibodies against the ACE2-binding interface of the RBD — the region most likely to confer sterilising neutralisation — while avoiding non-neutralising IgG against NTD, S2, and non-conserved spike regions that may mediate ADE. Prefusion-stabilised spike trimers (HexaPro with six Pro substitutions; 2P variant with K986P/V987P; GSAS furin site mutation) maintain the RBD in an immunologically accessible "up" conformation, enriching vaccine-induced responses for protective neutralising epitopes. RBD-only nanoparticle antigen constructs further focus the immune response by eliminating NTD and S2 from the immunogen entirely.

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8.2. Lipid Nanoparticle mRNA Vaccines

LNP-mRNA vaccines represent the most clinically validated nano-engineered coronavirus platform. BNT162b2 and mRNA-1273 use ionisable lipid nanoparticles (~80–200 nm) to deliver modified mRNA encoding prefusion-stabilised spike. Ionisable lipids (ALC-0315 in BNT162b2; SM-102 in mRNA-1273) adopt protonated cationic states at endosomal pH for mRNA complexation and neutral states at physiological pH, reducing systemic toxicity. ADE advantages of LNP-mRNA include: (i) antigen is prefusion spike with neutralising epitope focus; (ii) vaccination-induced IgG has core-fucosylated Fc glycoforms (unlike natural infection-induced afucosylated IgG with higher FcγRIIIa affinity); (iii) transient, localised spike expression avoids prolonged sub-neutralising antibody windows. Clinical data from hundreds of millions of LNP-mRNA vaccine recipients confirm absence of ADE, validating the antigen design and delivery strategy.

8.3. Virus-Like Particle Platforms

Virus-like particles (VLPs) are self-assembling protein nanostructures that mimic virion geometry without containing infectious nucleic acid. Heterologous scaffold systems (ferritin, I53-50, I3-01 scaffolds) allow site-directed conjugation of coronavirus RBD monomers or trimers at defined positions, creating multivalent nanoparticle RBD arrays with 8, 12, 20, or 60 antigen copies per particle. These architectures exploit BCR crosslinking principles (optimal epitope spacing 10–30 nm) to generate high-avidity, high-titre RBD-specific nAb responses with enrichment for ACE2-blocking antibody lineages. Since VLPs contain no Fc-activating material and present only the ACE2-binding face of the RBD, they minimise stimulation of antibody lineages associated with ADE risk.

8.4. Biodegradable Polymeric Nanoparticles (PLGA/Chitosan)

PLGA nanoparticles (100–500 nm) provide biodegradable antigen encapsulation with tunable hydrolytic degradation kinetics for sustained antigen release over days to weeks. This depot effect extends germinal centre B cell exposure to antigen, promoting deep affinity maturation and long-lived memory without requiring adjuvant scheduling. Chitosan nanoparticles (100–600 nm) offer additional advantages as mucosal delivery vehicles: chitosan is mucoadhesive, transiently opens tight junctions, and is intrinsically adjuvanting, facilitating dendritic cell antigen sampling and induction of secretory IgA (sIgA). Critically, mucosal sIgA (dimeric IgA) does not engage FcγRs on macrophages and therefore cannot mediate classical ADE — making intranasal chitosan nanoparticle vaccines inherently ADE-safe by design. Animal model studies with intranasal chitosan-spike formulations demonstrate sIgA responses at the respiratory mucosa that neutralise virus at the portal of entry before systemic FcγR-expressing immune cells are encountered.

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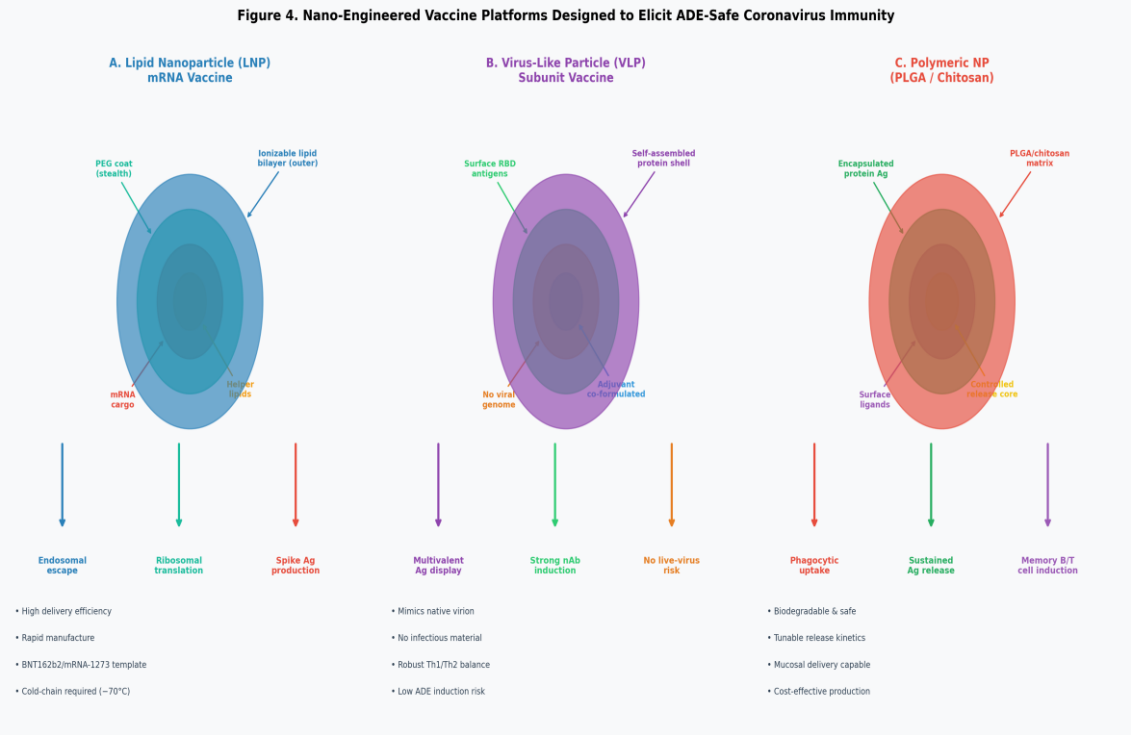

Figure 4. *Nano-engineered vaccine platforms for ADE-safe coronavirus immunisation. Panel A: LNP-mRNA vaccines deliver modified mRNA encoding prefusion-stabilised spike via ionisable lipid endosomal escape; generate core-fucosylated IgG1 nAbs. Panel B: Virus-like particles and nanoparticle-displayed RBD arrays present multivalent neutralising epitopes in geometrically optimised configurations for BCR crosslinking and high-titre nAb induction. Panel C: PLGA/chitosan polymeric nanoparticles provide biodegradable, tunable antigen release with mucosal delivery capability; sIgA induction avoids classical ADE pathway entirely.*

Table 4. Comparative Nano-Engineered Vaccine Platform Evaluation for ADE-Safe Coronavirus Vaccination.

Platform	Antigen Type	Size Range	Adjuvant?	ADE Risk Mitigation	Stage/Examples
LNP-mRNA	Encoded prefusion spike	80–200 nm	No (self-adj)	Selective nAb1 induction; core-fucosylated IgG Fc; brief Ag expression	Approved: BNT162b2, mRNA-1273
Virus-Like Particle	RBD/spike multimer	20–100 nm	Often co-formulated	No Fc-activating material; high nAb density; no Fc-triggering genome	HPV/HepB approved; CoV pre-clinical
PLGA NP	Protein/peptide subunit	100–500 nm	MPL, CpG	Sustained release prevents sub-nAb surge window; Th1 bias	Pre-clinical CoV; FDA-approved platforms
Chitosan NP	Mucosal protein Ag	100–600 nm	Intrinsic	Mucosal sIgA induction; sIgA does NOT engage FcγR → no ADE	Pre-clinical; intranasal route
Self-assembling NP	Ferritin-RBD, I3-01 scaffold	10–50 nm	Alum/AS01B	Precise epitope control; avoids immunodominance	Pre-clinical (HexaPro, SpFN, I53-50)

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				shift to non-nAb regions	

Table 4. Comparative evaluation of nano-engineered vaccine platforms. ADE risk mitigation mechanism, antigen type, and clinical/pre-clinical stage are compared across five platform classes. nAb, neutralising antibody; LNP, lipid nanoparticle; PLGA, poly(lactic-co-glycolic acid).

9. ADE in Comparative Perspective: Evidence Across Viral Families

Table 2. ADE Across Major Pathogenic Viruses: Mechanisms, Target Cells, and Clinical Significance.

Virus	Family	ADE Mechanism	Target Cell	Key Receptor(s)	Clinical Impact
DENV (Dengue)	Flaviviridae	Classical FcγR	Monocytes/Macrophages	FcγRIIa (CD32a)	DHF/DSS; ~25,000 deaths/yr; strongest clinical ADE evidence
SARS-CoV-2	Coronaviridae	Classical + Intrinsic	Alveolar Macrophages, Monocytes	FcγRIIa + ACE2 (cooperative)	COVID-19 cytokine storm; >6M deaths; both pathways implicated
SARS-CoV-1	Coronaviridae	Classical FcγR	Macrophages, DCs	FcγRI, FcγRII	In vitro ADE; vaccine-enhanced disease in animal models
FIPV (FCoV)	Coronaviridae	Classical FcγR	Peritoneal Macrophages	Feline FcγR	Fatal FIP; ADE is central, documented, and unavoidable mechanism
MERS-CoV	Coronaviridae	Putative Classical	Macrophages, T cells	DPP4 + FcγR (hypothetical)	In vitro evidence; uncertain in vivo significance
HIV-1	Retroviridae	Classical + Complement	CD4+ T cells, Macrophages	FcγRIII, CR3	Established in vitro; clinical relevance debated
Zika Virus	Flaviviridae	Classical FcγR	Placental macrophages, DCs	FcγRIIIa	Congenital Zika risk; cross-reactive DENV Ab implicated

Table 2. ADE across major viral pathogens. Dengue provides the strongest clinical evidence; SARS-CoV-2 exhibits mechanistic duality (extrinsic + intrinsic ADE); FIPV provides the most controlled natural coronavirus ADE model. DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; ARDS, acute respiratory distress syndrome; FIP, feline infectious peritonitis.

10. Challenges and Controversies in Coronavirus ADE

10.1. Clinical ADE in COVID-19: Evidence Assessment

The question of ADE clinical significance in COVID-19 has been one of the most contentious debates of the pandemic era. Proponents of ADE relevance cite: (i) in vitro demonstrations of antibody-facilitated SARS-CoV-2 infection of FcγR-expressing cells; (ii) correlation of non-neutralising anti-NTD/S2 antibody titres with severe disease; (iii) macaque model data

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demonstrating IgG-mediated exacerbation of lung pathology; and (iv) the FIPV precedent establishing fatal ADE in a structurally analogous coronavirus system.

Counter-arguments include: (i) no confirmed ADE case has been documented across hundreds of millions of mRNA vaccine recipients in phase III trials or post-authorisation surveillance; (ii) correlation between high neutralising antibody titres and protection is overwhelmingly robust; (iii) most in vitro ADE demonstrations employ non-physiological antibody concentrations or non-primary macrophage lines; and (iv) NK cell ADCC and cytotoxic T lymphocytes rapidly eliminate ADE-infected macrophages in vivo, limiting amplification potential. The weight of current evidence supports that mRNA vaccines have successfully avoided clinically significant ADE through prefusion-stabilised antigen selection, LNP delivery promoting neutralising IgG1 with favourable Fc glycosylation, and immunological endpoints consistently above the sub-neutralising ADE induction threshold.

10.2. Waning Immunity, Variants, and the ADE Threshold

A more nuanced concern involves scenarios where protective antibody titres wane below the neutralisation threshold against antigenically drifted variants — creating transient sub-neutralising conditions where ADE could theoretically operate. The emergence of SARS-CoV-2 variants with substantial RBD mutation (Omicron BA.1/BA.2/BA.4/BA.5 subvariants) resulted in significant reductions in neutralisation titres from ancestral-strain vaccination, raising the question of whether residual cross-reactive but non-neutralising antibodies could mediate ADE against heterologous variants. Bivalent booster vaccines targeting both ancestral and variant strains are designed in part to maintain nAb titres above this threshold.

11. Future Research Priorities

- Structural biology: Cryo-electron tomography of SARS-CoV-2–IgG–macrophage ternary complexes to directly visualise cooperative FcγR–ACE2 engagement geometry and endosomal sorting.
- Single-cell transcriptomics: sc-RNA-seq/ATAC-seq profiling of macrophages infected via ADE vs standard entry to map ADE-specific transcriptional signatures and identify targetable molecular checkpoints.
- FcγR-humanised animal models: Development of mice expressing human FcγRIIa (H131/R131 alleles) and FcγRIIb to enable in vivo ADE mechanistic studies not possible in standard murine models.
- FIPV vaccine re-engineering: Systematic evaluation of ADE-safe mucosal FIPV vaccine platforms (intranasal LNP-mRNA, VLP) as direct translational templates for ADE-proof human coronavirus vaccines.
- Nanomedicine platform comparison: Head-to-head comparison of LNP-mRNA, VLP, and PLGA nanoparticle vaccines in ADE-capable macaque and FIPV models, correlating antibody glycosylation profiles and nAb:non-nAb ratios with ADE protection.
- Fc engineering: Clinical evaluation of LALAPG and GASDALIE Fc-modified therapeutic mAbs to establish the therapeutic window between ADE risk and beneficial ADCC effector function.
- Polyherbal-nano interface: Investigation of plant-derived bioactive compounds (andrographolide from Andrographis paniculata; nimbin from Azadirachta indica; baeyer from Aegle marmelos) as nano-formulated adjunct immunomodulators capable of downregulating FcγR expression on macrophages to reduce ADE susceptibility while maintaining phagocytic function.
- Variant surveillance: Continuous monitoring of antibody cross-reactivity and neutralisation profiles against emerging SARS-CoV-2 variants of concern to identify ADE-permissive antibody configurations arising from immune imprinting or antigenic sin.

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12. Conclusions

Antibody-dependent enhancement in coronaviruses is a mechanistically nuanced phenomenon that extends across molecular, cellular, and comparative biological levels. The convergence of classical FcγR-mediated extrinsic ADE — best exemplified by the FIPV model — and novel intrinsic ADE mediated by FcγRIIb-SOCS-IFN-I suppression provides SARS-CoV-2 with multiple molecular interfaces through which the host antibody response can be co-opted to facilitate rather than restrict infection. The proposed cooperative FcγR–ACE2 entry model, while awaiting direct structural proof, is mechanistically coherent, geometrically feasible, and supported by accumulating experimental evidence.

Comparative veterinary immunology, and FIPV in particular, provides an irreplaceable model for coronavirus ADE research — the only natural host-pathogen coronavirus system in which ADE has been both unambiguously demonstrated as central to fatal pathogenesis and tested in the context of vaccination-enhanced disease. The lessons of FIPV — that sub-protective antibody titres can be worse than no immunity, that mucosal IgA strategies circumvent classical ADE, and that antiviral chemotherapy targeting viral polymerase is effective when immunoprophylaxis fails — represent directly applicable translational insights for human coronavirus medicine.

Nano-engineered vaccine platforms have demonstrated, through the remarkable clinical success of LNP-mRNA COVID-19 vaccines, that the theoretical ADE risk of coronavirus vaccination can be effectively mitigated through careful antigen design, delivery platform selection, and immunological outcome optimisation. Continued development of VLP, polymeric nanoparticle, and mucosal delivery systems will expand the coronavirus vaccine platform toolkit, while Fc engineering strategies for therapeutic monoclonal antibodies will improve the ADE safety profile of passive immunotherapy. Advancing the mechanistic understanding of coronavirus ADE at the intersection of molecular virology, structural immunology, comparative veterinary medicine, and advanced nanomedicine defines an exceptionally productive research space — and one that is critical for preparedness against future pandemic coronaviruses.

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