International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 11, Page 257-275.
https://doi.org/10.5281/zenodo.24578973

Review Article

Molecular Mechanisms of Ebola Virus Replication and Pathogenesis

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Ebola virus disease (EVD) is a severe zoonotic infection associated with recurrent outbreaks and substantial mortality. Its pathogenesis reflects coordinated viral and host processes that include glycoprotein-mediated entry, cytoplasmic transcription and genome replication, assembly and budding, and suppression or dysregulation of innate and adaptive immune responses. This narrative review synthesizes literature on Ebola virus structure and genome organization, the molecular stages of the replication cycle, viral strategies for interferon antagonism, and the host responses associated with systemic dissemination, vascular dysfunction, coagulopathy, and multiorgan injury. It also summarizes developments in monoclonal-antibody therapeutics, vaccines, and diagnostic approaches, alongside persistent challenges such as limited countermeasure coverage across ebolavirus species and survivor associated viral persistence. The literature indicates that disease severity cannot be explained by viral burden alone; it emerges from the interaction between viral replication, immune evasion, inflammatory imbalance, and tissue-specific injury. Further work should connect mechanistic studies with clinical outcomes and prioritize countermeasures that can be deployed rapidly and equitably during outbreaks.

Keywords: Ebola virus, Ebola virus disease, viral replication, pathogenesis, immune evasion, host–virus interactions

INTRODUCTION

Ebola virus disease (EVD) remains a major public-health concern because outbreaks can cause severe illness, place substantial pressure on health systems, and be difficult to control in resource-limited settings. Since the first recognized outbreaks in 1976, ebolavirus outbreaks have recurred, particularly in sub-Saharan Africa. The 2013–2016 West African epidemic was the largest recorded outbreak and had consequences extending beyond the affected countries, including imported cases and major disruptions to public health and livelihoods [1,2,3]. Understanding the molecular events that govern viral entry, replication, immune evasion, and tissue injury is essential for explaining disease severity and identifying opportunities for prevention and treatment [4,5]. This review summarizes Ebola virus biology, replication mechanisms, host–virus interactions, disease pathogenesis, and recent advances in countermeasures.

1.1 Global Burden

Ebola virus remains a persistent global health threat because outbreaks are recurrent, highly lethal, and difficult to control in resource-limited settings [2,6,7]. Between 2013–2016 West African epidemic was regarded as the most geographically fatal and extensive event on record, with tens of thousands of cases and over eleven thousand reported fatality cases, and it triggered concern well beyond Africa via imported cases across North America and Europe [1,2,8]. The repeated reemergence of Ebola outbreak across Africa has made Ebola long-term epidemic threats, rather being considered as one-time event [2]. For instance, outbreak in the West African epidemic remained as largest documented outbreak and is often defined as benchmark for preparedness and management of Ebola outbreaks for the upcoming days [1,3]. With respect to the ongoing outbreaks and unequal accessibility for countermeasures has always been treated Ebola as a current public health concern [3,7,9].

1.2 Epidemiology

Ebola is a zoonosis disease that begins typically from the spillovers into humans and then propagates via direct human-to-human transmissions via infected bodily fluids [6,10]. Sequence based outbreak analyses aided in reconstructing the origin and the overall transmission dynamics of West African epidemic, representing the spread from Guinea to the neighboring

nations and illustrating on how the genomic epidemiology tracks the viral movement and the resultant variations observed during sustained transmission [1].

- Zoonotic emergences is central for the Ebola epidemiology, especially fruit bats considered as most likely reservoir [10].
- Human transmission occurs primarily via direct contact with body fluids and from the infected individuals or their remains [6,10].
- Viral sequencing has helped clarify transmission chains and genetic variation during the 2013–2016 outbreak [1,2].

1.3 Clinical Importance

Ebola virus disease is clinically crucial since it rapidly progresses, resulting in the development of multiorgan dysfunction, disordered coagulation, vascular instability and high mortality, which could eventually overwhelm both the local health systems as well as with the international response capacity [4,5,11]. Severe disease reflected by combination of widespread viral dissemination and it severely causes damage to the host responses, which includes tissue injury, cytokine storm, myeloid dysfunction, lymphocyte loss and sepsis-like systemic pathology [4,11,12].

Table 1: Key Clinical Features of Ebola Virus Disease and Their Molecular Correlates.

Clinical Dimension	Main Features	Molecular/Pathophysiologic Basis
Acute severity	Hemorrhagic fever, shocks, organ failure	High viral replication and dissemination 4,11
Immune dysfunction	Cytokine storm, impaired antigen presentation, lymphocyte losses	Myeloid dysregulation and inflammatory injury 11,12
Coagulation injury	Bleeding and vascular leak	Disordered coagulation and dysregulation of host gene 4,13

1.4 Why Molecular Understanding Is Essential

Understanding Ebola virus at the molecular level is important because disease progression depends on viral and host mechanisms governing entry, immune evasion, RNA synthesis, virion release, and tissue injury. These mechanisms may reveal targets for prevention and treatment [7,14,15]. Recent investigations sharpened the view via showing EBOV utilises phase separated inclusion bodies for RNA synthesis, which depends on specific polymerase–leader RNA interactions for de novo replication, hijacks the host factors like CAD and PKA-CREB1 for supporting genomic replication followed by suppression of interferon signalling via VP35 and VP30, and it regulates budding via c-Abl1-dependent VP40 phosphorylation [5,13,14,16,17,18].

Entry and fusion depends on the multistep host-assisted processes, which includes with endocytosis, endosomal cleavage, NPC1 engagement, and membrane fusion [14].

Replication & transcription process relies on the specialized inclusion bodies, host metabolic/ signaling cofactors and phosphorylation state of VP30 [10,13,16].

Immune evasion results in enabling of uncontrolled viral propagation via interferon antagonism, glycoprotein-mediated immune subversion and antigen-presentation defects [1,6].

This review examines the molecular basis and life cycle of Ebola virus, from attachment and entry through transcription, genome replication, assembly, budding, and release. It also summarizes the roles of viral proteins and proviral host factors [14,15]. Furthermore, this review examines on how the replication mechanisms intersects with the pathogenesis, particularly with respect to interferon suppression, inflammatory and cell-death pathways, soluble glycoprotein

biology, post-translational regulation, coagulation abnormalities, defective genomes, followed by implications for antiviral and host-directed countermeasure development [5,11,19].

2. Ebola Virus Biology

This section summarizes Ebola virus taxonomy, virion structure, and genome–protein organization to provide a foundation for understanding viral replication and disease.

2.1 Taxonomy and Classification

Ebola virus is a prototypic member of Ebolavirus genus within Filoviridae family, and placed within Mononegavirales order, consistent with its ~19 kb negative-sense RNA genome encoding seven core viral proteins that collectively facilitates direct viral entry, followed by replication, assembly, and ultimately countering via effective immune evasion mechanisms as well [21,22]. Ebola virus (EBOV) refers specifically to virus that are classified within Zaire ebolavirus species in Ebolavirus genus [20,21]. Recent reviews described that there are six recognized ebolavirus species, although the older summaries and from some of the comparative investigational analyses listed five, reflecting taxonomic updates rather than the biological dispute [21,23,24]. As majority of ebolaviruses infects humans, but Reston and Bombali differed in terms of the human pathogenicity and host range when considered [21,23]. Phylogenetic analyses reliably classified ebolaviruses via coding their complete genomes and each of seven protein genes [25]. In addition from comparative genomics showed functional domains and conserved gene order across Filoviridae despite there are notable sequence divergences between the genera [26].

2.2 Virion Structure

Ebola virions are enveloped, pleomorphic, and usually filamentous, although circular, U shaped, and figure-6 forms also occur [21,27,28]. Their diameter is relatively uniform at about 80–98 nm, whereas length is highly variable, with typical particles near 800–1000 nm and occasional filaments extending many micrometers [15,24,27]. The virion contains a host-derived lipid envelope studded with GP spikes and a central helical nucleocapsid that packages the RNA genome [15,29].

2.3 Genome Organization

The Ebola genome is a linear, non-segmented, single-stranded negative-sense RNA molecule of about 19 kb [15,21,30]. Its gene order is conserved as 3′-NP-VP35-VP40-GP-VP30-VP24-L-5′, flanked by leader and trailer regions that contain promoter and replication signals [15,27]. Conserved untranslated regions border each gene and carry transcription start and stop signals that regulate sequential viral transcription [15].

- The GP gene is exceptional because it contains overlapping reading frames and undergoes transcriptional editing [21,31].
- GP editing yields multiple products, including full-length GP, sGP, ssGP, and Δ-peptide precursors or derivatives [15,21].
- Comparative genomics indicates that sequence variation is concentrated in GP, NP, and L, while overall genome organization remains stable [26,31].

2.4 Seven Viral Proteins

The seven canonical proteins are NP, VP35, VP40, GP, VP30, VP24, and L [15,22,24]. NP is the most abundant nucleocapsid protein and is essential for RNA encapsidation, transcription, replication, genome packaging, and nucleocapsid assembly [32,33]. VP35 acts as a polymerase

cofactor and also suppresses interferon responses, while VP30 functions as a transcription activator whose phosphorylation state helps regulate the transcription-replication balance [25].

VP40 is the primary matrix protein and drives virion assembly and budding at the plasma membrane, and its expression alone can generate virus-like particles [26,27]. GP is the only surface exposed viral protein and mediates host-cell attachment and entry, while also existing in secreted forms produced by RNA editing [25,31]. VP24 contributes to nucleocapsid architecture and antagonizes host immunity by blocking STAT1 nuclear transport, whereas L is the RNA dependent RNA polymerase that, together with NP, VP35, and VP30, is sufficient for viral transcription and replication [25,28].

Together, taxonomy, virion architecture, genome layout, and the coordinated functions of the seven viral proteins define the core biology of Ebola virus.

3. Molecular Mechanisms of Ebola Virus Replication

3.1 Viral Attachment

Ebola virus attachment begins when the viral glycoprotein engages host surface attachment factors rather than a single universal plasma-membrane receptor

[34,35]. Reported attachment factors include TIM-1, DC-SIGN, TAM-family receptors, and phosphatidylserine-recognizing pathways that support the virus's broad cell tropism [34,35,36]. Newer evidence also identifies CXCR4 and SLC39A9 as GP-binding host factors that can enhance early attachment [35,37].

3.2 Host-Cell Entry

After attachment, Ebola virus is internalized primarily through macropinocytosis into the endosomal system [34,35,38]. Entry depends on host endocytic machinery, including PIK3C3 kinase activity, which is required for efficient virion internalization [35]. Ebola entry is multistep and host-factor-rich rather than direct plasma-membrane fusion [14,39,40].

3.3 Endosomal Processing

Within acidified endosomes or lysosomes, host cysteine proteases cleave GP, trimming the glycan cap and mucin-like regions and exposing the receptor-binding domain [34,35,39]. Cathepsin B and cathepsin L are the main proteases most often implicated, although the exact proteolytic route can vary by cell type [21,35]. Cleaved GP then becomes competent to engage NPC1, the essential intracellular receptor for productive entry [21,39,40].

3.4 Membrane Fusion

NPC1 binding is required for Ebola membrane fusion and genome release from late endosomal compartments [21,35,39]. Fusion triggering occurs predominantly in Rab7-positive endosomes, and proteolytically primed GP must interact with NPC1 for lipid mixing to proceed [39]. Evidence remains nuanced after NPC1 engagement: one study suggests cathepsins are still needed after triggering to permit fusion-pore formation and cytoplasmic entry, whereas another argues that NPC1 alone is not sufficient and that an additional factor is required for full fusion activation [39,40].

3.5 Viral Transcription

Once the ribonucleoprotein complex reaches the cytoplasm, the negative-sense genome serves as the template for mRNA synthesis by the L polymerase with VP35 and VP30 [16,17,41]. NP associated RNA is the transcription template, and primary transcription occurs in the cytoplasm [16,21]. VP30 is a key transcription activator, and its phosphorylation state regulates the balance between transcription and replication; phosphorylated VP30 suppresses transcription by weakening promoter-cofactor function [21,42].

3.6 Genome Replication

Genome replication requires NP, VP35, and L, whereas VP30 is additionally required for transcription [16,41]. During replication, NP encapsidates both genome and antigenome, protecting RNA and forming functional nucleocapsid templates [16,21]. Structural work shows that de novo replication by the Ebola polymerase is directed by the 3′ leader sequence, whose bent RNA conformation in the L–VP35–RNA complex is required for efficient initiation [17].

3.7 Inclusion Bodies as Replication Factories

Ebola RNA synthesis occurs in cytoplasmic inclusion bodies, which act as replication factories and sites of nucleocapsid formation [14]. NP alone can seed inclusion body formation, but NP– VP35 interactions are central to linking inclusion-body assembly with RNA synthesis . These compartments also recruit host factors, including CAD, STAU1, NXF1, SMYD3, and importin-α7, showing that viral replication depends on concentrated host support within inclusions [16].

3.8 Assembly

Assembly begins with nucleocapsid formation in the perinuclear cytoplasm, followed by transport toward plasma-membrane budding sites [38]. NP forms the core NP–RNA helix, while VP24 and VP35 bind externally and regulate nucleocapsid assembly, intracellular transport, and infectious virion production . VP30 also associates with nucleocapsid-like structures, and its phosphorylation appears to facilitate this association without clearly controlling later transport [42].

3.9 Budding

Budding occurs mainly at the plasma membrane, where VP40 acts as the central matrix organizer [38]. VP40 is critical for transporting nucleocapsids to the cell surface and incorporating them into virions, likely through functionally important NP–VP40 interactions [41]. GP is trafficked through the secretory pathway to the plasma membrane and contributes to particle formation, while VP40 and GP together also promote phosphatidylserine exposure that may support filamentous virion morphogenesis [36,38].

3.10 Host Regulation of Replication

Ebola replication depends heavily on host pathways involved in metabolism, trafficking, and membrane dynamics [14,16]. CAD supports viral transcription and replication through pyrimidine synthesis after recruitment into inclusion bodies by NP, while CXCR4 promotes entry and also limits excess GP through reticulophagic degradation to improve viral fitness [16,37]. Host regulation also intersects with stage transitions, because VP24 and VP40 can reduce transcription/replication efficiency as nucleocapsids convert into assembly-competent forms, helping shift the virus from RNA synthesis toward virion production [41].

A detailed stepwise replication cycle and the viral and host factors that control each transition is shown in Table 2, as the literature converges on entry, RNA synthesis, inclusion-body organization, assembly, and budding as the major mechanistic stages 15,17 .

Table 2: Stepwise Mechanisms of Ebola Virus Replication

Replication Stage	Main Viral Factors	Main Host Factors	Core Mechanism	Key Evidence / Notes
Attachment	GP	Cell-surface carbohydrate and phosphatidylserine receptors	Virus first binds host cell surface attachment factors through GP, enabling uptake [15]	Reviews place attachment as the first stage, but the supplied set gives limited receptor-level detail compared with later entry steps [43]
Host Cell Entry	GP	Macropinocytic machinery	Internalization occurs primarily through macropinocytosis rather than direct plasma-membrane fusion [15]	Entry is part of a multistep endocytic route that precedes proteolytic priming and fusion 15
Endosomal Processing	GP1,2	Endosomal acidification, cathepsins	In endolysosomes, cathepsin cleavage processes GP, exposing the receptor binding state required for downstream entry 15	This processing is treated as a discrete checkpoint before receptor engagement and fusion [15]
NPC1-Dependent Fusion	GP1/GP2	NPC1	After cleavage, GP1 binds NPC1 and GP2 promotes membrane fusion, releasing the nucleocapsid into the cytosol 15	Fusion is essential because genome release requires endosomal receptor engagement, not surface fusion 15
Primary Transcription	L, VP35, VP30, NP	Host ribosomes for translation	The negative-sense genome is transcribed in the cytoplasm by the polymerase complex, generating viral mRNAs for protei production 15,17,44	Genes nearer the 3′ end are transcribed more efficiently, producing a transcription gradient 44
Transcription Control	VP30, VP35	—	VP30 acts as a transcription activator, and its phosphorylation state helps regulate the transcription–replication switch [42]	VP30's zinc-binding motif and conserved phosphorylation site are both linked to efficient transcriptional function 44
Genome Replication Initiation	L, VP35, NP	—	Replication begins only after sufficient viral protein accumulation and proceeds through full length antigenome synthesis followed by new genome synthesis 15	NP, VP35, VP30, and L form the canonical replication/transcription machinery, with VP30 more critical for transcription than for core replication 13,45
Replication Promoter Architecture	L-VP35-RNA complex	—	The EBOV replication promoter is bipartite, requiring a leader element plus a downstream element with correct spacing 46	Replication follows a rule of six at the promoter level: only insertions or deletions in multiples of six preserve activity 46

Replication Stage	Main Viral Factors	Main Host Factors	Core Mechanism	Key Evidence / Notes
Replication Start Site Logic	L, VP35	—	Ebolavirus polymerase uses an unconventional initiation mechanism, starting opposite the 3′-CCUGU motif even when terminal nucleotides vary 47	Variable 3′ ends and conserved 5′ ends support a distinctive replication strategy that can generate 3′ overhangs 47
Structural Basis of Replication	L, VP35, leader RNA	—	Structural work shows the 3′ leader RNA binds the polymerase template-entry channel in a stable bent conformation required for de novo replication 17	At least three base pairs can drive elongation once initiation is established 17
Inclusion Bodies	NP, VP35, VP30, L	Host factors recruited into inclusions	Viral protein accumulation drives formation of inclusion bodies, where secondary transcription and genome replication occur 15	CREB1 is recruited into viral inclusion bodies and used for replication, linking these structures to host-pathway hijacking 13
Host Support of Polymerase Function	VP35	AKIP1, PKA-CREB1, TRIM6, K63 polyUb	VP35 is a polymerase cofactor whose activity is strengthened by hijacked host pathways and ubiquitin-based regulation 13,48,49	Disrupting VP35–ubiquitin interactions or degrading unanchored polyUb reduces polymerase activity and infectious-virus replication 49
Nucleocapsid Assembly	NP, VP35, VP30, VP24, L	—	Newly synthesized genomes are packaged with nucleocapsid proteins before transport to budding sites [15]	Reston and Zaire EBOV nucleocapsid proteins are largely functionally exchangeable, indicating strong conservation of the replication complex 45
Budding	VP40, GP	c-Abl1	Assembly culminates at the plasma membrane, where VP40 organizes virion morphogenesis and particle release [15]	c-Abl1 promotes productive replication by phosphorylating VP40 at Y13; c-Abl1 knockdown or inhibition reduces VLP release and infectious replication 5
Cycle Kinetics	Entire viral program	Host-cell environment	In vitro modeling indicates the replication cycle includes a measurable eclipse phase, burst size, and virion clearance rate rather than being an instantaneous process 50	These quantitative parameters help constrain stage timing but do not assign durations to every molecular substep 50

4. Host–Virus Interactions and Immune Evasion

4.1 Innate Immune Antagonism

Innate immune recognition starts when the host pattern-recognition receptors detect viral nucleic acids and activate NF-κB, IRF3, IRF7, and interferon programs [51,52]. Ebola virus disrupts this early barrier via suppressing PRR function, especially RIG-I- and MDA5-linked sensing, and by blocking downstream interferon induction and signaling [51,53].

VP35 is the main innate immune antagonist at the sensing stage. It binds and shields dsRNA from host detection, blocks RIG-I access to viral RNA, disrupts the PACT–RIG-I interaction, and inhibits IRF3/IRF7 phosphorylation, thereby reducing type I interferon production [22,51,54]. VP35 also impairs dendritic-cell maturation and reduces induction of MHC and costimulatory molecules, weakening the bridge between innate and adaptive immunity [22,51].

VP24 acts later in the pathway by blocking interferon signaling rather than upstream sensing. It binds karyopherin-α family transport factors, prevents STAT-dependent nuclear trafficking, inhibits the JAK-STAT pathway, and suppresses interferon-stimulated antiviral responses [22,51,54]. Across reviews, VP24 and VP35 are consistently treated as the two principal Ebola proteins that blunt type I and type III interferon defenses [51,55]. VP35 hides viral dsRNA and blocks RIG-I pathway activation [22,51]. VP24 blocks interferon signaling through karyopherin-dependent STAT transport inhibition [22,54]. Together they enable unchecked viral replication by suppressing early antiviral defenses [6,56].

4.2 Immune Dysregulation

Ebola virus initially targets macrophages and dendritic cells, and this early tropism strongly shapes downstream pathogenesis [6,11,57]. Macrophage infection drives activation and inflammatory mediator release, while dendritic-cell infection and dysfunction compromise antigen presentation and T-cell priming [51,57].

Single-cell profiling in vivo adds mechanistic detail: conventional monocyte subsets are replaced by immature proliferative monocyte-lineage cells with reduced antigen-presentation capacity, while infected cells downregulate STAT1 and interferon signaling genes [12]. This helps explain why Ebola can trigger strong systemic inflammation yet still produce poor antiviral control [58,59].

A central driver of this inflammatory imbalance is GP-mediated immune modulation. EBOV GP activates TLR4-dependent NF-κB signaling in macrophages, induces inflammatory cytokines and chemokines, and recruits myeloid cells in vivo [60]. Comparative macrophage work shows this GP–TLR4 axis is much stronger with EBOV than with Reston virus, linking excessive GP-triggered inflammation to higher pathogenicity [59].

Table 3: Major Host–Virus Molecular Interactions Underlying Ebola Immune Evasion and Downstream Immune Dysfunction.

Factors	Main Molecular Interaction	Immunologic Consequence	Representative Evidence
Innate immune recognition	PRRs detect viral RNA, but EBOV suppresses RIG-I/MDA5 pathways	Weak early IFN induction	51,52,53
VP35	dsRNA shielding, PACT/RIG-I disruption, IRF3/7 inhibition	Blocks type I IFN production	22,51
VP24	KPNA binding and JAK-STAT interference	Blocks IFN signaling	22,51,54
GP-mediated modulation	GP activates TLR4 and inflammatory signaling	Cytokine amplification and myeloid recruitment	57,59,60
Macrophage infection	Early infection of macrophages	Systemic inflammatory activation	6,11,57
Dendritic cell dysfunction	VP35 inhibits maturation and costimulatory programs	Poor antigen presentation and T-cell activation	51
Cytokine storm	Dysregulated pro-inflammatory cytokine release	Tissue injury and multiorgan failure	6,11,61
Adaptive immune escape	sGP antibody decoy, GP masking, lymphocyte loss	Weak humoral and cellular control	12,54,56

4.3 Adaptive Immune Evasion

Adaptive immune failure appears secondary to early innate sabotage plus direct viral decoy mechanisms. Fatal infection is marked by poor adaptive activation, lymphocyte apoptosis or depletion, and impaired T-cell-dependent B-cell responses [57,61]. Single-cell data support this by showing lymphocytes upregulate apoptosis genes and decline in abundance during infection [12].

GP and sGP further weaken humoral recognition. Secreted glycoprotein can absorb anti-GP antibodies, and GP glycosylation and steric shielding reduce immune recognition of infected cells [22,54]. GP also masks HLA or MHC class I and II molecules at the cell surface, which further impairs immune detection [22,54].

The cytokine storm sits at the intersection of innate failure and adaptive collapse. Multiple reviews describe fatal EVD as a state of excessive, poorly timed pro-inflammatory cytokine release that damages immune cells and peripheral tissues and contributes to multiorgan failure [6,11,61,62]. GP appears to intensify this process: GP-containing virus-like particles exaggerate cytokine and chemokine expression in macrophages, and GP-bearing extracellular vesicles accumulate late in infection with enrichment of TLR4-related inflammatory mediators [57]. sGP acts as an antibody decoy that diverts anti-GP responses [54,56].

GP masking reduces recognition of HLA/MHC molecules on infected cells [22,54]. Lymphocyte loss and poor APC function blunt effective adaptive immunity [12,51,61].

Taken together, the evidence supports a coordinated immune-evasion program in which VP35 blocks sensing, VP24 blocks signaling, and GP reshapes inflammation and antibody recognition. That combination explains why Ebola can produce both severe inflammation and profoundly ineffective antiviral immunity [7,61]. Ebola virus pathogenesis begins in myeloid cells, spreads systemically through blood and lymph, and kills through immune dysregulation, vascular injury, coagulopathy, and multiorgan failure.

5. Molecular Basis of Ebola Pathogenesis

Ebola virus disease follows a fairly consistent pathobiological sequence from initial infection to disease severity, with strong agreement that early infection of mononuclear phagocytes, uncontrolled viral replication, and dysregulated host responses are the core drivers [2,4,63]. Evidence across human studies, animal models, pathology reviews, and newer tissue-resolved datasets also supports organ-specific contributions from liver, spleen, kidney, lung, adrenal, gastrointestinal, and vascular compartments [64,65,66].

5.1 Initial Infection

Ebola virus initially infects macrophages and dendritic cells, which are repeatedly identified as the earliest target cells after host entry [6,11,65,67]. Infection begins after exposure through dermal injury or mucosal contact in humans, and index cases are usually linked to zoonotic spillover before human-to-human transmission dominates [6,65,67,68].

Early infection disables host defense because infected dendritic cells and macrophages suppress effective antiviral immunity while supporting viral replication [6,69]. Broad cell tropism follows quickly, with productive infection reported in monocytes, macrophages, dendritic cells, fibroblasts, hepatocytes, adrenal cells, endothelial cells, epithelial cells, and Kupffer cells [11,66,67].

5.2 Systemic Spread

Systemic dissemination is driven by infected monocytes, macrophages, and dendritic cells migrating from the entry site to regional lymph nodes and then amplifying infection through lymphatic and hematogenous spread [2,11,65,70]. High viremia is a central feature of severe disease, and widespread dissemination across tissues has now been shown in both classic reviews and newer whole-body or multi-tissue analyses [2,4,64].

Systemic spread appears to intensify as innate and adaptive immune responses are suppressed or mistimed, allowing unrestricted replication and secondary infection of target organs [2,6,68,70]. Tissue-resolved primate data further show that viral variation can emerge early and differ across compartments, implying that dissemination is biologically dynamic rather than uniform across organs [64,71].

5.3 Organ Injury

Direct organ injury reflects both viral cytopathic effects and host-mediated damage [11,70,71]. The liver is one of the most consistently implicated organs, with hepatocellular necrosis, elevated liver enzymes, and impaired synthesis of coagulation factors contributing to hemorrhagic complications [11,63,70].

Kidney injury is also common and appears multifactorial, involving hypovolemia, cytokine mediated toxicity, acute tubular damage, and sometimes direct infection of renal tissue [11,65,67]. Gastrointestinal, adrenal, splenic, and pulmonary involvement all contribute to systemic decline, with GI losses driving dehydration, adrenal injury impairing blood pressure regulation, and lung injury reflecting systemic inflammation, edema, or direct infection [65,67,69].

Newer human omics and imaging studies suggest that organ injury is not only a consequence of viral burden but also of aberrant host programs, including pancreas-associated enzymes, neutrophil-linked tissue damage, lymphoid depletion, and altered tissue-connectivity gene expression [4,64,66].

5.4 Vascular Leakage and Coagulopathy

Vascular leakage is a major mechanism of severe Ebola disease, with consensus that vascular dysfunction arises from inflammatory mediators, endothelial dysfunction, and later direct endothelial injury [63,70,72]. Infected and activated monocytes and macrophages release cytokines, chemokines, nitric oxide, and other mediators that damage vascular integrity and promote leak [11,69,73].

Hemorrhage is not universal, but when present it reflects a combination of capillary leak, endothelial injury, thrombocytopenia or microthrombosis, and reduced hepatic production of coagulation factors [11,65,73]. Multiple reviews describe disordered coagulation or disseminated intravascular coagulation as a hallmark of severe disease, although some mechanistic details remain contested [4,55,67].

One interpretation emphasizes endotheliopathy with release of inflammatory cytokines and unusually large von Willebrand factor multimers, leading to disseminated intravascular microthrombosis and hepatic coagulopathy [73]. Complementary cell-based work shows that Ebola virus-like particles can directly perturb endothelial and macrophage metabolism, consistent with host-cell dysfunction contributing to leak and clotting failure even beyond productive infection [74].

5.5 Multiorgan Failure and Disease Severity

Multi-organ failure is the dominant terminal syndrome in fatal Ebola virus disease [11,67,75]. Fatal disease combines high viral replication, systemic inflammation, tissue damage, and coagulation abnormalities [4,63,70]. Severe outcomes correlate with high viremia and dysregulated immune responses, whereas lower viremia tends to track with less organ dysfunction and survival [65,71]. Patients who die show stronger interferon and inflammatory pathway upregulation, including higher burdens of defective viral genomes in one recent human study [76].

Disease severity appears to reflect the balance between viral expansion and host control rather than any single lesion [65,70,71]. Severe cases show sepsis-like molecular signatures, lymphopenia, cytokine storm, vascular breach, and progressive organ dysfunction, whereas survivors mount more effective and specific immune responses and clear viremia [4,65,66].

Overall, the molecular basis of Ebola virus pathogenesis is a staged process: early myeloid infection enables systemic dissemination, dissemination drives organ tropism and injury, and immune dysregulation amplifies vascular leakage, coagulopathy, and multiorgan failure.

Disease severity is therefore best understood as the cumulative outcome of viral burden, tissue specific injury, and a maladaptive host response.

Table 4: Stepwise Table of the Molecular Basis of Ebola Virus Pathogenesis from Initial Infection to Terminal Disease.

Pathogenesis Stage	Main Molecular / Cellular Basis	Main Consequence	Evidence
Initial infection	Ebola virus first infects macrophages and dendritic cells, the main early target cells among the mononuclear phagocyte system	Early local replication and immune-system disruption	6,19,77,78
Innate immune evasion	Viral proteins VP35 and VP24 suppress host interferon pathways, and immune evasion is a core driver of pathogenesis 19,22	Weak antiviral control permits unchecked replication	6,22,52
Dendritic cell dysfunction	Infection of dendritic cells prevents normal maturation and limits their ability to activate antigen-specific T-cell responses 19,52,79	Impaired adaptive immune priming	52,79
Systemic dissemination	Infected macrophages and dendritic cells migrate to lymph nodes, then spread virus to other tissues, producing high viremia 6,19	Body-wide dissemination of infection	6,19,65
Broad tissue tropism	Ebola productively infects many cell types, including monocytes, macrophages, dendritic cells, endothelial cells, hepatocytes, fibroblasts, and adrenal cortical cells 19,77,80	Multiple organs become direct viral targets	19,65,77
Macrophage-driven inflammation	Pathogenesis is partly dictated by viral replication in macrophages, which can produce strong inflammatory responses and more cytokines in more virulent infection settings 6,52,78	Severe inflammatory amplification	6,52,78
Cytokine storm	Early disease is marked by an uncontrolled cytokine storm with broad pro-inflammatory mediator release 6,20,81	Immune dysregulation and tissue injury	20,52,81

Pathogenesis Stage	Main Molecular / Cellular Basis	Main Consequence	Evidence
GP-mediated pathogenesis	Ebola glycoproteins have pathogenic roles beyond entry, including soluble and shed forms that contribute to immune modulation and virulence 79,80	Enhanced immune subversion and host cell injury	6,52,80
Lymphocyte loss	Severe Ebola is characterized by lymphopenia and lymphoid depletion, even though lymphocytes are not major productively infected cells 52,65,81	Collapse of effective adaptive immunity	52,81
Organ injury	Direct viral replication plus host mediated damage injure the liver, kidney, endothelium, spleen, and adrenal tissues 2,19,77	Progressive organ dysfunction	65,75
Vascular leakage	Viral hemorrhagic fever pathogenesis includes vascular permeability and endothelial dysfunction, promoted by uncontrolled replication and inflammatory responses 52,81	Plasma leakage, hypovolemia, shock tendency	52,58,81
Coagulopathy	Severe disease includes coagulation abnormalities and coagulopathy, likely linked to inflammatory injury and liver dysfunction 52,58,81	Hemorrhage and thrombo inflammatory complications	52,75,81
VP40-associated pathogenesis	VP40 is essential for virion budding, and extracellular or exosomal VP40 can damage immune-cell viability and contribute to bystander pathology 81,82	Added immune-cell injury beyond direct infection	81,82
Host-factor dependence	Ebola pathogenesis depends on host machinery and host–virus protein interactions, including post-translational control of viral protein function 19,79	Efficient replication and pathogenic signaling	19,79
Terminal disease	Fatal Ebola culminates in multiorgan failure with severe bleeding complications after rapid systemic spread and immune dysregulation 6,65,75	Death in severe cases	14,75,83

Across the literature, the most consistent model is that Ebola pathogenesis starts with myeloid cell infection, progresses through immune evasion and systemic spread, and ends in vascular dysfunction, coagulopathy, and organ failure [6,52]. Lower-ranked but relevant papers reinforce this same sequence by adding roles for dendritic-cell migration, host-factor dependence, glycoprotein-mediated immune subversion, and VP40-associated bystander damage [19,80,81].

FIGURE 2. Molecular basis and mechanism of Ebola virus (EBOV) replication and pathogenesis. Abbreviation: EBOV - Ebola virus, EVD - Ebola virus disease, GP – Glycoprotein, NP – Nucleoprotein, VP24, VP30, VP35, VP40 - Viral proteins 24, 30, 35, and 40, L protein - RNA dependent RNA polymerase, RNP-Ribonucleoprotein complex, TIM-1 - T-cell immunoglobulin and mucin domain-containing protein-1, DC-SIGN - Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-Integrin, L-SIGN- Liver/Lymph Node-Specific Intercellular Adhesion Molecule-3-Grabbing Integrin, NPC1 - Niemann–Pick disease type C1 receptor, RIG-I Retinoic Acid-Inducible Gene-I - MDA5 Melanoma Differentiation-Associated Protein 5, IRF3 - Interferon Regulatory Factor 3, IFN-I - Type I interferon, STAT1 - Signal Transducer and Activator of Transcription 1, ISGs - Interferon-Stimulated Genes, sGP - Soluble glycoprotein, TNF-α - Tumor Necrosis Factor-α, IL-1β - Interleukin-1β, IL-6 - Interleukin-6, IL-8 - Interleukin-8, MCP-1 - Monocyte Chemoattractant Protein-1, IFN-γ - Interferon-γ, DIC - Disseminated Intravascular Coagulation, PT - Prothrombin Time, PTT - Partial Thromboplastin Time

The upper middle panel summarizes the Ebola virus replication cycle. Viral entry is initiated through GP-mediated attachment to host cell surface attachment factors, including T-cell immunoglobulin and mucin domain-containing protein-1 (TIM-1), Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-Integrin (DC-SIGN), liver/lymph node specific intracellular adhesion molecule-3-grabbing integrin (L-SIGN), lectins, and other attachment molecules. Internalization primarily occurs through macropinocytosis, followed by endosomal trafficking where GP undergoes proteolytic cleavage by host cathepsins. Cleaved GP subsequently binds the intra-

cellular receptor Niemann–Pick C1 (NPC1), triggering membrane fusion and release of the viral ribonucleoprotein (RNP) complex into the cytoplasm. Viral transcription and genome replication are mediated by the viral polymerase complex within specialized cytoplasmic replication compartments, after which newly synthesized nucleocapsids are transported to the plasma membrane for virion assembly and VP40-mediated budding, producing mature infectious virions.

The lower left panels illustrate the principal mechanisms by which Ebola virus suppresses host innate immunity. VP35 inhibits activation of the retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) signaling pathways by preventing

activation of interferon regulatory factor-3 (IRF3), thereby suppressing production of type I interferons (IFN-I). VP24 interferes with the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway by preventing nuclear translocation of phosphorylated STAT1, thereby inhibiting transcription of interferon-stimulated genes (ISGs). In addition, soluble glycoprotein (sGP) and shed GP act as immune decoys by binding host antibodies, diverting immune recognition, and reducing effective neutralization of membrane-associated GP.

The central lower panel demonstrates early viral dissemination following infection of primary target cells, including macrophages, monocytes, and dendritic cells. Productive replication within these immune cells facilitates systemic viral spread while simultaneously inducing uncontrolled production of pro-inflammatory cytokines and chemokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), and interferon-γ (IFN-γ), resulting in a cytokine storm that amplifies tissue injury and immune dysregulation.

The right panel summarizes the major pathological manifestations of Ebola virus disease. Excessive inflammatory responses and direct GP-mediated endothelial injury result in vascular leakage and endothelial dysfunction, leading to hypotension and circulatory collapse. Concurrent hepatic injury impairs synthesis of coagulation factors, while activation of coagulation pathways contributes to disseminated intravascular coagulation (DIC), thrombin generation, and prolonged prothrombin time (PT) and partial thromboplastin time (PTT). Additional organ damage involving the kidneys and adrenal glands further contributes to metabolic imbalance, circulatory failure, and immune dysfunction. Collectively, these pathological processes culminate in multiorgan failure, septic shock-like syndrome, and death in severe Ebola virus disease.

6. Recent Advances in Ebola Research

Recent Ebola virus research has advanced most clearly in therapeutics, vaccines, diagnostics, and outbreak preparedness, while major gaps remain for Sudan ebolavirus, severe disease, and survivor-associated viral persistence [65,84,85].

6.1 Therapeutic Progress

The most important clinical advance is that two monoclonal antibody therapies, MAb114 and REGN-EB3, reduced 28-day mortality more than ZMapp in the randomized PALM trial conducted during the Democratic Republic of the Congo outbreak [86]. In that trial, mortality was 35.1% with MAb114 and 33.5% with REGN-EB3, compared with about 50% in the ZMapp groups, establishing antibody therapy as the first clearly effective antiviral treatment for acute Ebola virus disease [65,86,87].

These gains are substantial but incomplete. Survival remains poor in patients with high viremia or advanced disease, and shorter symptom duration before admission strongly correlates with better outcomes, showing that earlier diagnosis and treatment still matter even in the antibody era [86,87,88]. Current approved therapies are largely EBOV-specific, so pan-species antibody strategies are still needed for Sudan, Bundibugyo, and other human-pathogenic ebolaviruses [87,88,89].

Recent preclinical work has widened the therapeutic pipeline beyond licensed antibodies. Candidate approaches include glycoprotein inhibitors, protease-related small molecules, and host-targeted strategies focused on NPC1-dependent entry, including bispecific antibodies that bind both viral glycoprotein and NPC1 and have shown efficacy in murine models [87]. Computational screening and artificial intelligence are also being used to prioritize antiviral

compounds, although no small-molecule drug directed at Ebola viral proteins has yet cleared clinical trials [87,90,91].

6.2 Vaccine Development

Vaccine research has also progressed rapidly since the 2013–2016 West African epidemic, which accelerated candidates that had previously been at early stages of development [89,92,93]. The landmark product is Ervebo (rVSV-ZEBOV), the first FDA-approved Ebola vaccine, which generates a rapid antibody response within 14 days after a single dose and has been central to ring-vaccination strategies in later outbreaks [87,89,94].

A second major advance is the heterologous Ad26.ZEBOV/MVA-BN-Filo regimen, approved in 2020 for adults and children at least 1 year old and designed to broaden and extend protection through a prime-boost strategy [91,94]. More broadly, the vaccine field now includes replication competent and non-replicating viral vectors, DNA platforms, and virus-like particle approaches, with several candidates showing protective efficacy in animal models and advancing into clinical development [92,94].

Key challenges remain. Existing licensed vaccines mainly target Zaire ebolavirus, while outbreaks caused by SUDV highlight the need for cross-protective and outbreak-ready vaccines for multiple species [87,94]. Important unanswered questions include durability beyond about one year, safety in immunocompromised populations, cold-chain logistics, product stability, multi dose follow-up, and optimal deployment strategies for healthcare workers and exposed contacts [87,89,90,94].

6.3 Diagnostic and Response Advances

Table 5: Recent Diagnostic Advances in Ebola Virus Research and Their Main Trade-Offs.

Advance	Main Finding	Limitation	Evidence
RT-PCR platforms	Remain the diagnostic standard in recent outbreaks	Centralized testing delays isolation and treatment	65,95
Rapid diagnostic tests	Faster and easier to deploy in low resource settings	Negative tests still need molecular confirmation	95
New antigen tests	sGP-based lateral-flow assay achieved 100% specificity and 85.7% sensitivity	Validation focused on Zaire Ebola virus	101
CRISPR diagnostics	SHERLOCK with HUDSON enabled extraction-free, field-deployable detection	Operational scale-up still determines impact	102

Diagnostic science has shifted from accuracy alone toward speed, deployability, and access. Molecular assays such as Real-Star Altona and Cepheid remain sensitive, but point-of-care tools such as LAMP, antigen assays, and CRISPR platforms aim to shorten time to isolation in settings where laboratory infrastructure is limited [95]. This matters because preparedness gaps remain structural as well as technical, including limited specimen access, weak community level testing capacity, fragmented funding, and insufficient incentives to sustain diagnostics between outbreaks .

Recent research has also sharpened understanding of pathogenesis and persistence. Human systemic immune-response data remain limited, but post-2014 work has improved understanding of disease progression and survivor-associated viral persistence, including Ebola RNA detected in breast milk hundreds of days after infection and prolonged detection in semen and breast milk in survivor follow-up studies [65,84]. These findings help explain why flare-ups can re-emerge after apparent outbreak control and why One Health surveillance, survivor care, and cross-sector coordination are now central to preparedness [84,85].

Overall, recent advances in Ebola virus research are real and clinically meaningful: effective EBOV antibodies now exist, licensed vaccines can blunt transmission, and diagnostics are becoming more field-deployable. The main frontier is extending these gains to multiple ebolavirus species, earlier case detection, persistent infection in survivors, and affordable access during future outbreaks.

7. Limitations and Future Research Directions

Work on the molecular mechanisms of Ebola virus replication and pathogenesis is now mechanistically richer, but the biggest limitations are still incomplete

structural resolution, partial life-cycle models, limited human tissue-level data, and poor translation from mechanism to broadly deployable antivirals. These gaps persist partly because EBOV research depends heavily on BSL-4 containment and surrogate systems, which capture only subsets of the viral life cycle [11,12].

The most striking gap is the mismatch between strong mechanistic detail for polymerase biology and weak evidence linking those mechanisms to human disease heterogeneity or approved small-molecule treatments. High-resolution work now shows that EBOV de novo replication depends on a specific 3′ leader RNA bend stabilized in the polymerase entry channel, while other studies show an unconventional replication mechanism with 3′ overhangs and back-priming-like features, but these insights have not yet produced clinically available polymerase-targeting drugs [17,47,96]. The same translation gap appears in computational discovery, where incomplete structural coverage, small and imbalanced datasets, and limited experimental validation still constrain progress [7].

Dependence on biosafety level 4 (BSL-4) facilities remains a major research constraint, while BSL-2 minigenome and virus-like-particle (VLP) systems model only selected stages of infection [11,12]. Full understanding on polymerase regulation is still incomplete because transcriptase-replicase switching, domain coordination, and full-length structural organization remain unresolved in parts [96]. Many host dependencies are identified, but their precise causal roles are still fragmentary, including CAD, GSPT1, UPF1, and hypusinated eIF5A-VP30 regulation [16,96,97]. In addition, pathogenesis models still lack a unified map from infected-cell events to multiorgan injury, coagulopathy, and cell fate, especially in humans [4,11].

7.1 Future Research Directions

Future work should connect molecular mechanism to disease phenotype using integrated human and animal datasets. Single-cell profiling shows infected cells downregulate STAT1 and interferon signaling while upregulating pro-viral genes, and multi-omics studies argue that progress now depends on integrating PBMC transcriptomics with plasma proteomics, lipidomics, and metabolomics and with better knowledge of infected organs and secreted factors [4,12].

A second priority is deeper study of underresolved viral products and persistence biology. sGP has multiple proposed roles in pathogenesis and countermeasure escape, but its functions still need definitive testing, while survivor-associated persistence in immune-privileged tissues remains a major unresolved mechanism behind recrudescence and long-term sequelae [8,82,98].

A third priority is mechanism-driven antiviral development beyond antibodies. Host-directed strategies are attractive because they can raise the barrier to resistance and potentially enable broad-spectrum activity, but they require more exact host–virus mechanism maps; promising directions include CAD-linked pyrimidine supply, GSPT1 degradation, polyamine hypusination targeting, and better-defined VP40 trafficking interfaces such as Sec24c [15,16,96,97,99].

Finally, future models should incorporate viral diversity and defective genomes. Comparative transcriptomics suggests epidemic mutations did not clearly attenuate pathogenicity in vivo despite some in vitro fitness differences, and patient studies now indicate defective EBOV genomes correlate with viral load, interferon activation, and fatal outcome, which complicates simple assumptions that defective genomes are therapeutically beneficial [76,100].

Future work should integrate structural and cell-biological models, validate findings in human relevant systems, and translate mechanistic insights into scalable antiviral strategies that address viral diversity and persistent infection.

CONCLUSION

Ebola virus disease results from the interaction of viral replication, immune evasion, systemic dissemination, and dysregulated host responses. The viral glycoprotein mediates cell entry, while the nucleoprotein and polymerase complex support RNA synthesis and replication. VP35 and VP24 interfere with antiviral interferon responses, and GP-associated inflammatory effects contribute to immune dysfunction. Together, these processes can promote vascular leakage, coagulation abnormalities, tissue injury, and multiorgan failure. Advances in monoclonal antibody treatment, vaccination, and molecular diagnostics have improved the tools available for controlling EVD, but important gaps remain, particularly for

ebolavirus species not covered by existing countermeasures and for survivor-associated viral persistence. Future research should connect molecular findings with clinical outcomes, validate promising targets in appropriate models, and support countermeasures that are safe, accessible, and effective across outbreak settings.

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Cite: Joseph Selva Kumar, Renose Banu, Subathra. M., Punitha. D., Tharanya. P., Molecular Mechanisms of Ebola Virus Replication and Pathogenesis, Int. J. Med. Pharm. Sci., 2026, 2 (11), 257-275. https://doi.org/10.5281/zenodo.24578973