IJIE
International Journal of Innovation and Entrepreneurship

Ebola Virus: Host Cell Entry Mechanisms, Immune Evasion Strategies, and Therapeutic Interventions

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Submitted: 26 February 2025, accepted: 18 March 2025, published: 24 March 2025

Abstract: The Ebola virus (EBOV) is a highly lethal pathogen responsible for Ebola virus disease (EVD), posing significant threats to global public health. This review examines the entry mechanisms, immune evasion strategies, and therapeutic advancements targeting EBOV. The virus infiltrates host cells via receptor-mediated binding, macrophage phagocytosis, and endosomal membrane fusion, processes that facilitate viral replication and subsequent disease progression. We analyze EBOV's immune evasion tactics, particularly its suppression of innate and adaptive immune responses through viral proteins such as VP35 and soluble glycoprotein (sGP). Current therapeutic strategies are also discussed, including prophylactic vaccines (e.g., Ervebo® and Zabdeno®) that effectively prevent infection and monoclonal antibody therapies (e.g., ZMapp, Ebanga®, and INMAZEB®) undergoing clinical optimization. Despite progress in EBOV treatment, persistent challenges such as global inequities in vaccine distribution and development hinder effective disease control. Future research should prioritize elucidating host–pathogen interactions to refine therapeutic targets, developing broad-spectrum vaccines to address viral diversity, and enhancing international collaboration to ensure equitable access to treatments in resource-limited, outbreak-prone regions.

Keywords: Ebola virus; viral invasion mechanisms; immune evasion; vaccine development

How to cite: Liu, X. Ebola Virus: Host Cell Entry Mechanisms, Immune Evasion Strategies, and Therapeutic Interventions. *Int. J. Innov. Entrep.*, 2025, 1(1): 5; doi:10.56502/IJIE1010005.

1. Introduction

Between December 2013 and March 2016, West Africa experienced the largest, longest, and deadliest outbreak of Ebola virus disease (EVD) to date, caused by the Ebola virus (EBOV). This outbreak affected over ten countries, including Guinea and Liberia, with 28,652 confirmed cases and 11,325 deaths (Ohimain and Silas-Olu, 2021). EVD is a zoonotic disease transmitted from animals to humans and spreads through direct contact with bodily

fluids or contaminated surfaces. Symptoms include fever, severe gastrointestinal distress, and multi-organ failure, with mortality rates historically ranging between 25% and 90%, depending on healthcare access and viral strain (Jacob et al., 2020).

EBOV, a member of the Ebolavirus genus in the Filoviridae family, is a non-segmented, single-stranded RNA virus. Its genome encodes seven structural proteins critical for viral replication and host immune evasion, including glycoprotein (GP), nucleoprotein (NP), and matrix protein VP40 (Jain et al., 2021). To fight against the EBOV, experimental vaccines and therapeutics such as monoclonal antibodies and viral vector-based vaccines were deployed on an emergency basis. However, challenges in development, testing, and regulatory approval hindered their timely and effective implementation (Ohimain and Silas-Olu, 2021).

This review examines the molecular mechanisms of EBOV entry into host cells, its pathogenesis, and strategies to evade innate and adaptive immune responses. We also evaluate current vaccines and therapeutics, alongside persistent challenges in global vaccine equity and outbreak preparedness.

2. Entry and Pathogenesis Mechanism of Ebola Virus

This section outlines the entry mechanisms of EBOV into host cells and the pathogenic consequences of viral replication.

The EBOV entry process involves sequential steps: receptor binding, membrane fusion, ribonucleoprotein (RNP) complex formation, glycoprotein (GP)-mediated immune evasion, and matrix protein VP40-driven virion assembly. EBOV initially binds to host–cell receptors such as C-type lectins (CLECs) or phosphatidylserine (PtdSer) receptors. Viral internalization occurs primarily via macropinocytosis, after which endosomal proteases (e.g., cathepsin L/B) cleave the viral glycoprotein, exposing the receptor-binding domain (RBD). Subsequent interaction with the Niemann-Pick C1 (NPC1) receptor on endosomal membranes triggers membrane fusion, releasing the RNP complex into the cytoplasm to initiate replication (Moller-Tank and Maury, 2015; Yu et al., 2017).

The accumulation of EBOV in host tissues drives severe pathogenesis, characterized by sudden-onset fever, hemorrhage, and multi-organ failure. The virus preferentially infects immune cells such as macrophages and dendritic cells, impairing innate immunity. This results in a cytokine storm marked by excessive secretion of pro-inflammatory cytokines (e.g., IL-6 and TNF-α), which exacerbate immune cell apoptosis and tissue damage (Falasca et al., 2015). Furthermore, EBOV disrupts endothelial integrity in critical organs (e.g., the kidney, liver, and spleen), increasing vascular permeability and causing fluid leakage into interstitial spaces, i.e., a hallmark of hypovolemic shock in fatal cases.

3. Immune Evasion Mechanisms of Ebola Virus

Following entry and replication in host cells, EBOV employs sophisticated immune evasion mechanisms to avoid detection and elimination by the host immune system. EBOV primarily subverts both innate and adaptive immunity through viral proteins such as VP35 and soluble glycoprotein (sGP), which disrupt interferon (IFN) production and signaling. These proteins enable sustained viral replication and pathogenesis within the host.

Audet and Kobinger (2015) identified eight EBOV-encoded proteins, four of which (VP35, sGP, GP1,2, and VP24) directly antagonize host immune responses. Figure 1 illustrates EBOV's evasion of innate immunity via VP35, VP30, and VP24. VP35 inhibits IFN production by blocking the RIG-I/MDA-5 signaling pathway, preventing the activation of antiviral genes. VP30 suppresses RNA silencing by interfering with host RNA interference (RNAi) pathways, a critical defense against viral RNA. VP24 impedes IFN signaling by sequestering karyopherin α, thereby blocking the nuclear import of STAT1/STAT2 and inhibiting the expression of IFN-stimulated genes. Additionally, surface GP mediates receptor binding and immune evasion by masking viral epitopes, while matrix protein VP40 inhibits dendritic cell maturation and cytokine secretion (Audet and Kobinger, 2015; Misasi and Sullivan, 2014). Collectively, these mechanisms enable EBOV to evade immune surveillance and establish systemic infection.

EBOV also evades adaptive immunity, which is manifested in both humoral and cell-mediated immune

responses. Figure 2 shows two key evasion mechanisms in adaptive immunity: humoral immunity suppression and cellular immunity disruption. EBOV subverts humoral immunity through viral proteins such as sGP and GP, which interfere with antibody neutralization by masking viral epitopes or redirecting antibodies away from their targets (Figure 2a). EBOV disrupts dendritic cell (DC) function, impairing antigen presentation and T cell activation (Figure 2b). Specifically, EBOV targets three critical pathways in T cell activation. First, while the initial antigen recognition via major histocompatibility complex (MHC)-T cell receptor (TCR) interactions remains intact, EBOV selectively inhibits downstream co-stimulatory and survival signals. Second, the absence of co-stimulatory accessory molecules (e.g., CD80/CD86) on infected DCs prevents the clonal expansion of $CD4^+$ T cells, rendering helper functions ineffective. Third, EBOV induces the apoptosis of $CD8^+$ T cells, which are responsible for cytotoxic responses, thereby crippling cellular immunity. Through these mechanisms, EBOV suppresses the effector functions of key immune cells, enabling systemic immune evasion (Falasca et al., 2015).

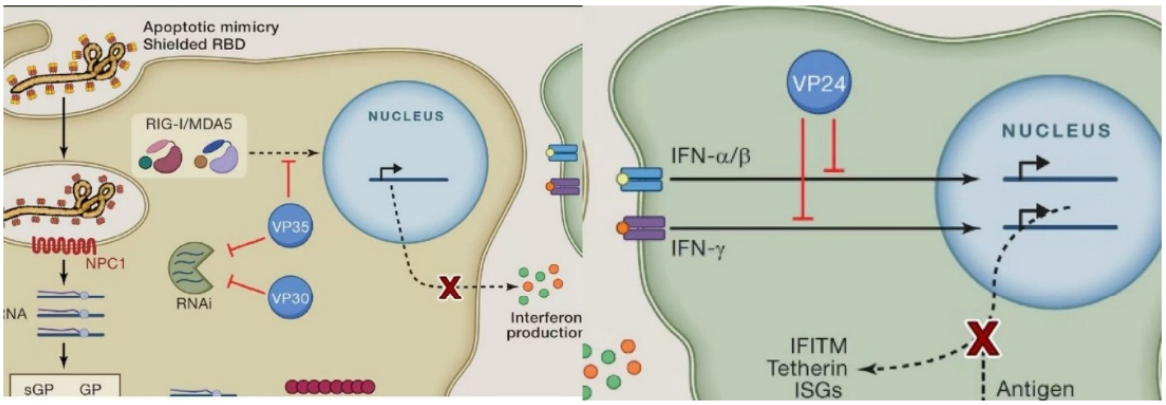

Figure 1: The immune avoidance mechanisms of EBOV. Figure reproduced with permission from (Misasi and Sullivan, 2014). Copyright @ 2014 Elsevier Inc.

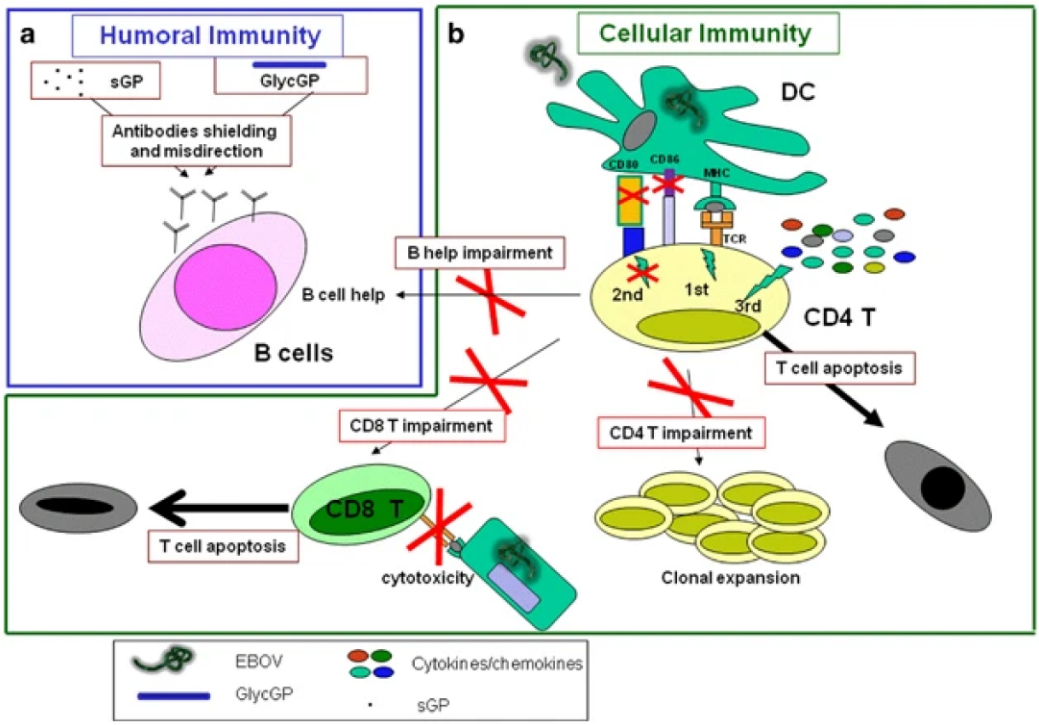

Figure 2: Two routes of EBOV evasion mechanism. Figure reproduced with permission from (Falasca et al., 2015). Copyright @ 2015 Springer Nature.

4. Treatment of Ebola virus disease

This section reviews current treatment strategies for EVD, focusing on vaccine development, therapeutics, and systemic challenges in global implementation.

EVD has caused intermittent outbreaks in Central and West African countries, characterized by an unpredictable high fatality rate. Following the devastating 2013–2016 EVD epidemic in West Africa, efforts to develop targeted vaccines intensified significantly (Tomori and Kolawole, 2021). To date, several vaccine candidates have advanced to maturity, undergoing preclinical and human clinical trials. These candidates can be categorized into distinct groups, including virus-like particle-based vaccines, DNA vaccines, recombinant whole-virus vaccines, and replicating or non-replicating viral vector vaccines (Malik et al., 2023). Two vaccines have been licensed and deployed for use: Ervebo® (rVSV-ZEBOV) and the two-dose regimen Zabdeno® (Ad26.ZEBOV) followed by Mvabea® (MVA-BN-Filo). Merck's Ervebo vaccine, which utilizes an attenuated vesicular stomatitis virus (VSV) vector engineered by truncating the cytoplasmic tail of the VSV glycoprotein, received approval from the FDA and EMA in 2019. Of the nine EVD vaccine candidates under development, two have been fully licensed, while the remainder are in various phases of clinical trials (Tomori and Kolawole, 2021).

Vaccines are effective in preventing EVD but are no longer beneficial once infection occurs. To treat infected individuals and alleviate symptoms, therapeutic agents have been developed to combat EVD. Although treatment options remain limited, three primary drugs are currently used: ZMapp, Ebanga (ansuvimab-zykl), and INMAZEB (atoltivimab/maftivimab/odesivimab). Each drug exhibits distinct therapeutic mechanisms and efficacy profiles. For example, ZMapp, a monoclonal antibody cocktail, is the first-line treatment for Ebola, achieving a 91.2% survival rate under the current standard of care. Ebanga, administered as a single intravenous (IV) dose of 50 mg/kg, has demonstrated a mortality rate of 35.1% in clinical trials and is recommended for patients with cardiovascular complications. INMAZEB, delivered via IV at 3 mL/kg, reduces mortality by 17% in EVD patients (Sivanandy et al., 2022). However, these therapies are associated with side effects such as fever, tachycardia, diarrhea, vomiting, hypotension, and chills.

In addition to vaccines and therapeutics, supportive care including the maintenance of vital signs and symptom management, plays a critical role in reducing mortality rates. Vaccine development faces several challenges. A primary hurdle is identifying a suitable vaccine candidate. An effective vaccine must be immunogenic, capable of eliciting a robust immune response, and cross-protective. Ideally, it should confer rapid protection post-administration, retain efficacy post-exposure, and offer broad-spectrum or multivalent coverage against all Ebola virus species and strains (Malik et al., 2023; Tomori and Kolawole, 2021). Developing a fully functional vaccine meeting these criteria remains a significant technical challenge.

Another critical challenge lies in global health equity. Although advancements in EVD therapeutics have been achieved in high-resource settings like the United States, these treatments remain inadequately accessible in regions most affected by the disease. This disparity stems from financial incentive structures prioritizing pharmaceutical development and stockpiling for markets such as the U.S., rather than addressing the urgent needs of endemic areas. Such a focus contradicts principles of equitable global health access. Furthermore, the absence of effective multilateral coordination and unified leadership has hindered the establishment of systematic frameworks to ensure streamlined drug development, scalable production, and equitable distribution (Torreele et al., 2023).

In summary, EBOV enters host cells via specific molecular mechanisms, evades immunity through proteins like VP35 and sGP, and causes severe pathogenesis. While vaccines (e.g., Ervebo®) and therapeutics (e.g., ZMapp) represent significant advancements, challenges in technical development, equitable distribution, and global collaboration limit their impact.

5. Conclusions and outlook

In conclusion, this paper reviews the entry mechanisms, immune evasion strategies, and treatment approaches for the EBOV.

The Ebola virus enters host cells through a multi-step process involving receptor binding, internalization,

protease cleavage, membrane fusion, and RNP release. Following entry, viral replication triggers a cytokine storm, leading to systemic immune dysregulation, tissue damage, and multi-organ failure. EBOV employs viral proteins such as VP35 and sGP to subvert innate and adaptive immune responses, enhancing its survival. Prophylactic vaccines like Ervebo® (rVSV-ZEBOV) and Zabdeno® (Ad26.ZEBOV) have demonstrated efficacy in preventing infection, while therapeutics such as ZMapp, Ebanga® (ansuvimab-zykl), and INMAZEB® (atoltivimab/maftivimab/odesivimab) alleviate symptoms and improve survival rates. However, persistent technical challenges in vaccine development and global inequities in healthcare access hinder effective disease control.

Despite significant advancements in vaccines and therapeutics, critical gaps remain. Future research should prioritize elucidating the molecular interplay between EBOV and the host immune system during viral entry and immune evasion. Current vaccines predominantly target specific EBOV strains, lacking broad efficacy against diverse variants or emerging species. Developing pan-ebolavirus vaccines capable of neutralizing multiple strains is essential to address viral evolution. Furthermore, given the limited healthcare infrastructure in endemic regions, cost-effective antiviral drugs and monoclonal antibody therapies must be optimized for scalability and accessibility.

Finally, strengthening international collaboration is imperative to mitigate disparities in resource distribution. High-income nations, such as the United States, should leverage their technological and clinical expertise to support outbreak-prone regions, ensuring equitable access to vaccines, therapeutics, and advanced treatment protocols during emergencies.

Funding: This research received no external funding.

Conflicts of Interest: The author declares no competing financial interests.

References

Audet, Jonathan, and Gary P Kobinger. 2015. Immune evasion in ebolavirus infections. *Viral Immunology* 28: 10–18. [CrossRef] [PubMed]

Falasca, Laura, Chiara Agrati, Nicola Petrosillo, Antonino Di Caro, Maria R. Capobianchi, Giuseppe Ippolito, and Maria Piacentini. 2015. Molecular mechanisms of Ebola virus pathogenesis: Focus on cell death. *Cell Death & Differentiation* 22: 1250–59.

Jacob, Shevin T., Ian Crozier, William A. Fischer, Angela Hewlett, Colleen S. Kraft, Marc-Antoine de La Vega, Moses J. Soka, Victoria Wahl, Anthony Griffiths, Laura Bollinger, and et al. 2020. Ebola virus disease. *Nature Reviews Disease Primers* 6: 13. [CrossRef] [PubMed]

Jain, Sahil, Ekaterina Martynova, Albert Rizvanov, Svetlana Khaiboullina, and Manoj Baranwal. 2021. Structural and functional aspects of Ebola virus proteins. *Pathogens* 10: 1330. [PubMed]

Malik, Sumira, Shristi Kishore, Sagnik Nag, Archna Dhasmana, Subham Preetam, Oishi Mitra, Darwin A León-Figueroa, Aroop Mohanty, Vijay Kumar Chattu, and Marjan Assefi. 2023. Ebola virus disease vaccines: Development, current perspectives & challenges. *Vaccines* 11: 268. [PubMed]

Misasi, John, and Nancy J Sullivan. 2014. Camouflage and misdirection: The full-on assault of ebola virus disease. *Cell* 159: 477–86.

Moller-Tank, Sven, and Wendy Maury. 2015. Ebola virus entry: A curious and complex series of events. *PLoS Pathogens* 11: e1004731. [CrossRef] [PubMed]

Ohimain, Elijah Ige, and Daniel Silas-Olu. 2021. The 2013–2016 Ebola virus disease outbreak in West Africa. *Current Opinion in Pharmacology* 60: 360–65. [CrossRef] [PubMed]

Sivanandy, Palanisamy, Pee Hui Jun, Lai Weng Man, Ng Sin Wei, Nicole Foo Kar Mun, Celestine Ang Jia Yii, and Charissa Cheah Xiao Ying. 2022. A systematic review of Ebola virus disease outbreaks and an analysis of the efficacy and safety of newer drugs approved for the treatment of Ebola virus disease by the US Food and Drug Administration from 2016 to 2020. *Journal of Infection and Public Health* 15: 285–92. [CrossRef] [PubMed]

Tomori, Oyewale, and Matthew Olatunji Kolawole. 2021. Ebola virus disease: Current vaccine solutions. *Current Opinion in Immunology* 71: 27–33. [PubMed]

Torreele, Els, Yap Boum, Ismael Adjaho, Franck Guy Biaou Alé, Sal Ha Issoufou, Geza Harczi, Chibuzo Okonta, and Piero Olliaro. 2023. Breakthrough treatments for Ebola virus disease, but no access—What went wrong, and how can we do better? *The Lancet Infectious Diseases* 23: e253–e258. [PubMed]

Yu, Dong-Shan, Tian-Hao Weng, Xiao-Xin Wu, Frederick XC Wang, Xiang-Yun Lu, Hai-Bo Wu, Nan-Ping Wu, Lan-Juan Li, and Hang-Ping Yao. 2017. The lifecycle of the Ebola virus in host cells. *Oncotarget* 8: 55750. [CrossRef]