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An expanded hypothesis: The role of ascorbate and glucose in the intracellular processes and immunobiology of Ebola virus haemorrhagic fever

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Abstract

The opposing effects of glucose and ascorbate transport on physiological processes may help explain Ebola virus disease pathophysiology. The virus impairs intracellular interferon (IFN) signalling. High plasma glucose levels contribute to oxidative stress and may also inhibit IFN signalling. Conversely, ascorbate may counteract the virus-mediated IFN blockade and interfere with viral budding. Dysregulation of glucose and ascorbate homeostasis may contribute to the pathophysiology of Ebola virus haemorrhagic fever by promoting oxidative stress, activation of the nuclear factor kappa B (NF-κB) pathway, and a cytokine storm. Hyperglycaemia commonly occurs in critically ill patients with Ebola virus haemorrhagic fever. Therefore, haemorrhagic fever syndrome could be understood as a state of oxidative stress driven by hyperglycaemia, NF-κB pathway activation, and inflammatory cytokines. A potential treatment strategy would focus on administering ascorbate and glutathione, together with glucose or insulin as appropriate, to maintain normal, stable plasma glucose levels and combat oxidative and inflammatory stress.

Keywords: Ebola virus; Ascorbate; Glucose; Interferon; Nuclear factor kappa B; Oxidative stress; Interleukin-6; CYPP450

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1. Introduction

Regarding Ebola virus (EBOV) infection, there has not yet been a comprehensive biological explanation of the severity and systemic nature of the clinical manifestations or of the underlying pathophysiology. A substantial body of experimental evidence is now available, providing important descriptive and molecular insights and also shedding light on key factors involved in the disease process. In a previous opinion article by Chicano Wust[1], the pathophysiological processes associated with viral haemorrhagic fever, particularly those caused by Filoviruses, were discussed, with a focus on viral entry and the interaction of the viral glycoprotein (GP) in the virion envelope with host factors.[1] That article proposed a pivotal role for glucose and ascorbate in the pathophysiological changes occurring during infection, involving dysregulation of glucose and ascorbate homeostasis, subsequent oxidative stress, activation of the nuclear factor kappa B (NF-κB) pathway, and a cytokine storm resulting in injury to multiple tissues.

This article, which complements the previously published work, focuses on viral factors, including VP24, VP40, and nucleoprotein (NP), that act within intracellular compartments following viral entry. The article discusses pathological and molecular processes, such as virus-mediated suppression of interferon (IFN) signalling and the interplay between the virus and the immune system in relation to other pathophysiological regulatory systems. These include the role of the cytochrome P450 (CYP450) enzyme system in hepatocytes and its interplay with virus-induced liver injury and suppression of the IFN response. The roles of glucose and ascorbate in the immune response and cellular redox state, as well as their influence on viral activity, are also examined, together with the interplay between viral infection, homeostasis, and the haemorrhagic fever syndrome. It is hypothesised that EBOV haemorrhagic fever (EBOVHF) represents a virus-driven state of oxidative stress caused by hyperglycaemia, NF-κB activation, and increased production of inflammatory cytokines.

1.1. Ebola Virus

As described in standard virology textbooks[2,3], the family Filoviridae, together with families such as Rhabdoviridae, Bornaviridae, Pneumoviridae, and Paramyxoviridae, belongs to the order Mononegavirales. Filovirions have an irregular, pleomorphic morphology. Filamentous particles may be branched, U-shaped, or folded into a spiral. They have a constant diameter of about 80 nm, while their length varies widely, reaching up to 14,000 nm. Marburg virus particles are generally approximately 665 nm long, and EBOV particles have a reported average length of approximately 805 nm.

The filamentous particles contain a helical nucleocapsid composed of the RNA genome and the components of the filovirus ribonucleoprotein complex: NP, polymerase cofactor VP35, transcriptional activator VP30, large protein L (RNA-dependent RNA polymerase), and ribonucleoprotein complex-associated protein VP24. VP30 is considered a minor NP and regulates viral replication and transcription. A viral envelope surrounds the nucleocapsid. The major matrix protein VP40 and the minor matrix protein VP24 are associated with the inner leaflet of the lipid envelope and with the protein components of the nucleocapsid. Viral GP is embedded in the viral envelope as a trimer and projects approximately 7 nm from the virion surface. GP is the only viral protein exposed on the virion surface. It is extensively modified by carbohydrate groups linked to amino acid residues through N- and O-glycosidic bonds. As a type I membrane protein, GP is anchored in the viral envelope through a hydrophobic transmembrane segment at its carboxyl terminus. GP consists of two subunits, GP1 and GP2, which mediate, respectively, interaction of the virion with the target cells (GP1) and fusion of the viral envelope with the endosomal membrane.

The EBOV GP mediates viral entry.[4–6] Several cellular factors have been described as mediators or enhancers of filovirus entry, including the following:

- Universal mammalian filovirus receptor: Niemann–Pick receptor of the endosomal compartment (NPC1). NPC1 is an essential intracellular receptor for filovirus entry and is located in the endosomal compartment. NPC1 expression in non-permissive reptilian cells confers susceptibility to filovirus infection.[7]
- Attachment factors: Several cell-surface molecules can facilitate the initial attachment and uptake of filoviruses.
    - The TAM family receptor tyrosine kinase AXL (Axl): Axl has been shown to enhance micropinocytosis of EBOV.[8]
    - T-cell immunoglobulin and mucin domain 1 (TIM-1; also known as hepatitis A virus cellular receptor 1) binds to the receptor-binding domain of the Zaire EBOV GP. Ectopic expression of TIM-1 in poorly permissive cells enhances EBOV infection by approximately 10- to 30-fold.[9]

Following attachment, filoviruses enter host cells predominantly through endocytic pathways, although micropinocytosis is considered an important route of entry. Within the acidic endolysosomal compartment, cathepsins B and L cleave GP1, removing the mucin-like subdomains and glycan cap and exposing the receptor-binding site.[3] The exposed GP1 receptor-binding site then engages domain C of NPC1.

As indicated above, TIM-1 binds directly to EBOV GP, but its principal physiological function is to bind phosphatidylserine residues on apoptotic cells through its immunoglobulin variable domain. Axl binds to growth arrest-specific 6 (Gas6), which in turn binds to phosphatidylserine. As proposed in the previous article[1], EBOV incorporates phosphatidylserine into its envelope, thereby exploiting apoptotic mimicry to facilitate recognition and uptake of viral particles by target cells. During viral budding, the VP40 matrix protein hijacks cellular scramblases, including XK-related protein 8 and transmembrane protein 16F, to promote phosphatidylserine incorporation into the viral envelope. Efficient budding of viral particles depends on functional phosphatidylserine, which is clustered by VP40 at sites of budding.[10,11]

Four viral proteins—NP, RNA-dependent RNA polymerase, VP30, and VP35—are core components of the viral replication and transcription machinery. EBOV VP40 is essential for viral budding.[12] As described by Kuroda *et al.*[13], EBOV VP24 and VP35 are key nucleocapsid components, with VP24 contributing to proper nucleocapsid assembly. VP35 can counter the IFN response induced during EBOV infection, inhibiting the phosphorylation and subsequent nuclear translocation of IFN regulatory factor 3 (IRF3).[14,15] Following the release of IFN from infected cells, IFN binds to IFN receptors on neighbouring cells, activating Janus kinase/signal transducer and activator of transcription (JAK/STAT)-dependent signalling pathways. VP24 can counter this activation by inhibiting STAT1 nuclear translocation. Activation of the JAK/STAT pathway induces the expression of IFN-stimulated genes (ISGs), whose products can directly restrict viral replication. However, EBOV has evolved additional countermeasures against ISG-mediated antiviral activity. For example, VP35 inhibits protein kinase R activation[16], whereas GP counteracts tetherin-mediated restriction of viral budding.[17] Budding filoviruses incorporate a portion of the plasma membrane, including phosphatidylserine, as well as the membrane-embedded GP1 and GP2 complexes that form the viral surface projections. Phosphatidylserine, which serves as a ligand for filovirus attachment factors such as TIM-1, is translocated from the inner leaflet of the plasma membrane to the outer leaflet of the viral envelope through cellular scramblase activity.[3]

1.2. Pathology of the Ebola virus haemorrhagic fever

According to the literature, the major clinical manifestations of EBOV disease include a maculopapular rash and mucosal haemorrhage. The disease initially presents with nonspecific symptoms, including fever, asthenia, diarrhoea, headaches, myalgia, arthralgia, vomiting, and abdominal pain. The disease may then progress rapidly, with outcomes ranging from recovery to death within approximately three weeks. Massive bleeding, fluid distribution disturbances, disseminated intravascular coagulation, and focal necrosis are observed in fatal cases. Arthralgia, asthenia, and neurological disorders, such as dysesthesias, may persist as sequelae during convalescence, which can last from weeks to months. The main clinical features of EBOVHF have been described in the available literature.[18–21]

Ebola virus has a broad cellular tropism and can infect a variety of cell types and tissues. During the early phase of infection, the virus targets dendritic cells, monocytes, and activated macrophages, and may also infect endothelial cells. However, endothelial damage during filovirus infection has been described without evidence of direct endothelial cytolysis, suggesting indirect mechanisms may contribute to vascular injury.[22] Histopathological studies have revealed frequent necrosis in the liver, spleen, and lymph nodes.[23] In the later stages of the illness, fluid distribution disturbances, extensive haemorrhage, and multiorgan failure may occur. Overall, the clinical manifestations and pathophysiological processes resemble those observed in septic shock.[21] Patients with fatal filovirus infection typically die with very high viraemia, an absence of mononuclear phagocytic infiltration at sites of infection, and little evidence of an effective humoral or T-cell-mediated immune response.[24] In addition, filoviruses have evolved mechanisms that enable them to counteract IFN's antiviral effects.

1.3. Interferons and the immune system: The pivotal role of interferons and interferon-induced antiviral response

Interferons are cytokines that are critical components of the first-line antiviral response by activating antiviral, antiproliferative, and immunomodulatory pathways. IFNs are classified into three main types (I, II, and III), based on receptor usage and structural characteristics. Type I IFNs include IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. Nearly all nucleated cells, including dendritic cells, produce them upon viral recognition. They induce an antiviral state in surrounding cells by degrading viral RNA and inhibiting protein synthesis. Type I IFNs also increase the expression of the major histocompatibility complex class I (MHC-I). IFN-γ represents the sole type II IFN and is produced mainly by activated T cells and natural killer cells. It is a key activator of macrophages, enhancing their ability to eliminate pathogens and tumour cells. It also increases MHC class II expression and links innate and adaptive immunity by promoting inflammatory responses. IFN-γ exerts several metabolic effects, modulating glucose metabolism at both the systemic and cellular levels to support optimal immune responses while restricting viral replication.[25,26] Type III IFNs are represented by the IFN-λ family. Similar to type I IFNs, they are produced early during infection, but their activity is more restricted because the IFN-λ receptor is expressed predominantly at epithelial barriers.

Interferon regulatory factor 3 is activated through specific signalling pathways, most notably the cyclic GMP-AMP synthase–stimulator of IFN genes axis, retinoic acid-inducible gene I-like receptors and toll-like receptors 3 and 4 (TLR3/4), which detect viral nucleic acids or infection-associated molecular signals. In the nucleus, IRF3 acts together with NF-κB and AP-1 to form an enhanceosome on the promoters of several target genes, thereby driving the expression of type I and type III IFNs. IFNs induce the

activation of JAK/STAT-dependent signalling pathways. As mentioned above, activation of JAK/STAT pathways induces ISGs. IFN-α, IFN-β, and IFN-ω use a common receptor to activate JAK1 and tyrosine kinase 2, leading to activation of STAT1 and STAT2. IFN-γ signals through the IFN-γ receptor to activate JAK1 and JAK2, which predominantly phosphorylate STAT1.

Toll-like receptor 3 and TLR4 are innate immune receptors that bridge innate and adaptive immunity. They recognise pathogens, trigger immune responses, and release inflammatory cytokines. TLR3 is localised primarily in the endosomal membrane, whereas TLR4 is expressed mainly on the cell surface of cells such as macrophages, neutrophils, and dendritic cells. TLR3 signals through the TIR-domain-containing adapter-inducing IFN-β (TRIF)-dependent pathway to induce the production of type I IFNs. TLR4 exhibits a dual signalling mechanism: at the plasma membrane, it activates the NF-κB pathway, whereas following endocytosis, it triggers the TRIF adapter pathway, leading to type I IFN production.

Acute inflammation induced by viral infection leads to a transient increase in proinflammatory cytokines, such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). TNF-α is a key inflammatory cytokine produced by macrophages, dendritic cells, and T cells, and it exerts widespread effects on glucose metabolism during viral infections.[27]

Interleukin-1 is a proinflammatory cytokine that is critical for immune activation and metabolic reprogramming.[25,28] It is produced in response to pathogen-associated molecular patterns and damage-associated molecular patterns. IL-1 is regulated by NF-κB signalling and inflammasome-mediated caspase-1 cleavage. Upon binding to its receptor, IL-1 activates mitogen-activated protein kinase and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathways, promoting glycolysis in immune cells. This involves upregulation of glucose transporter 1 (GLUT1) and glycolytic enzymes.

Interleukin-6 is another proinflammatory cytokine that significantly affects glucose metabolism.[25,29] It enhances hepatic gluconeogenesis by activating the JAK/STAT3 pathway in hepatocytes, increasing gluconeogenic enzyme expression and contributing to hyperglycaemia, which is most commonly observed in severe viral infections and cytokine storm syndromes.[25–30]

1.4. Cytochrome P450 enzymatic system in hepatocytes: The chemical defence and its relation with the immune system defence

According to Coutiño Rodriguez[31], CYP450 enzymes help organisms defend against chemically stressful conditions by metabolising various xenobiotics. They critically influence the organism's overall metabolic regulation. From a nuclear receptor regulation perspective, CYP450 enzymes are associated with the immune system. Both systems represent mechanisms for the biological and chemical recognition of self and non-self structures. Indeed, there is a high degree of homology between the cytochrome superfamily members, especially CYP450 2D6, CYP450 2D9, and the kappa chain of the γ-immunoglobulin (IgG).

Cytochrome P450 enzymes are monooxygenases that introduce a single oxygen atom into a substrate (RH) while reducing the second oxygen atom to water. One oxygen atom is reduced to water, while the other is incorporated into the substrate, forming a hydroxylated product (ROH). The oxidised substrate is then released, and the catalytic cycle is repeated, with the enzyme returning to its original oxidised ferric (Fe^{3+}) state.

Inflammatory cytokine levels can decrease the activity of several CYP450 isoforms. Conversely, CYP1 inhibition has been found to increase the expression levels of the stem cell factor receptor (c-Kit) and IL-22, while decreasing IL-17. Single-cell analyses showed that CYP1 inhibition particularly promoted $CD4^+$ helper T (Th) cells co-expressing c-Kit and IL-22.[32]

2. Methods

The method or workflow involved identifying the key concepts underlying the proposed hypothesis, focusing on the key role of the GLUT1 transporter and its interactions with ascorbate and glucose in EBOVHF pathophysiology. The identified concepts and findings were then connected, and an in-depth literature search was conducted using the Google Search tool to identify evidence supporting the proposed ideas and hypothesis. This approach was not based on the availability of multiple, extensive, or contradictory references. Rather, the relevant available data were considered limited, and literature findings were selected as clues to support the proposed hypothesis. This approach assumes that the scientific quality, prestige, and relevance of the publications provide a sufficient basis for considering their findings as a foundation for proposing new approaches and research opportunities.

3. Discussion of the literature-based evidence: An expanded hypothesis

3.1. The basis of the hypothesis

The previous article by Wust[1] analysed evidence supporting a pivotal role for glucose and ascorbate homeostasis in EBOV disease. Interestingly, erythrocyte expression of GLUT1, a transporter of glucose and dehydroascorbate

(DHA), has been associated with the inability to synthesise ascorbate and is restricted to species susceptible to filoviruses or considered natural reservoirs of these viruses, including primates, humans and fruit bats. This observation is underscored by the fact that GLUT1 is expressed in EBOV host species, including species susceptible to EBOV infection and used in experimental studies to reproduce aspects of EBOV pathogenesis and clinical symptoms in humans. GLUT1 currently has no recognised role in interactions with the EBOV GP. However, a possible implication has been suggested by the reported sequence homology[1] between EBOV GP and the GP of human T-cell leukaemia virus type 1, a retrovirus that uses GLUT1 as a receptor for viral entry. This possibility warrants further investigation. An interesting experimental approach to examine a potential role of GLUT1 in EBOV infection would be to assess the effect of GLUT1 inhibition on EBOV entry *in vitro*, using cytochalasin as a GLUT1 inhibitor. Because cytochalasin B exerts its inhibitory effect by docking at the positively charged endofacial pocket 3A of GLUT1,[25] mutagenesis of this site could be used to investigate its influence on interactions with EBOV GP and viral entry. Other mechanisms by which GLUT1 could indirectly influence EBOV pathophysiology may be more difficult to investigate. The interaction of EBOV GP with cellular factors such as TIM-1 or Axl tyrosine kinase is well established. The hypothesis presented in this work extends the proposed relationship between GLUT1 and EBOV GP to consider possible interactions between TIM-1 and Axl and glucose transport and metabolism, which warrant further experimental investigations. Given their respective physiological functions, TIM-1 is considered a stimulatory molecule for cell activation, whereas TIM-3 has inhibitory functions. Because TIM-3 has been reported to decrease GLUT1 expression in Jurkat T cells[1,33], TIM-1 may, by contrast, increase GLUT1 expression. This possibility requires experimental investigation. If TIM-1 enhances GLUT1 expression and glucose and ascorbate transport, viral interference with TIM-1 could disrupt its function and consequently alter GLUT1 expression or ascorbate and glucose transport. This would provide a potential connection between GLUT1 and glucose and ascorbate transport. Gas6–Axl receptor signalling has also been described as glucose-regulated in vascular smooth muscle cells. Based on this finding, a direct or indirect interaction between Axl and GLUT1 could be hypothesised, given that glucose may regulate the physiological function of Axl.[1,34] The hypothesis proposes the following sequence of events as a predictive model. Interaction or binding of EBOV GP to GLUT1, or to other functionally related proteins that also act as EBOV attachment factors or receptors, such as the Axl TAM receptor and TIM-1, could potentially disturb glucose and ascorbate availability in cells. This may be particularly relevant to lymphocytes and other immune cells with high glycolytic demands (Warburg effect).[35,36] Lymphocyte apoptosis is a relevant feature of EBOV infection. Lymphocytes require an adequate, continuous glucose supply to meet their energetic demands. Hypoglycaemia or hyperglycaemia can drive lymphocyte apoptosis. Transient hypoglycaemia may be a consequence of liver damage caused by the viral infection, as the liver is the main supplier of glucose to the plasma. Reduced availability of glucose and ascorbate to lymphocytes as a consequence of the proposed viral GP–GLUT1 interaction, together with effects on other related cellular factors, could represent an additional mechanism contributing to the observed lymphocyte apoptosis. Conversely, excessively high plasma glucose levels can promote oxidative stress and apoptosis.[37] Hyperglycaemia may dysregulate the mechanistic target of rapamycin signalling pathway, reducing survival signals, such as those mediated by the anti-apoptotic protein Bcl-2, while increasing the expression of pro-apoptotic proteins such as Bax and Bim. These changes may promote cytochrome c release and activation of the mitochondrial pathway. This provides another potential mechanism that could contribute to the marked lymphocyte apoptosis reported during EBOV infection.

According to the hypothesis, the ultimate consequence of EBOV GP interactions with host factors could be a hyperglycaemic state associated with high erythrocyte abundance in the blood and the extensive endothelial surface lining the vasculature, characterised by increased plasma glucose concentrations, low levels of ascorbate in the cells, and impaired glucose transport. Although numerous mechanisms have been proposed in the literature to explain EBOV pathophysiological changes, a comprehensive picture of the disease process remains lacking, and many of the proposed mechanisms remain incompletely defined. The hypothesis developed in the present article, with further consideration of the immunological implications of EBOV pathophysiology, proposes a virus-driven hyperglycaemic state accompanied by substantial oxidative stress that may govern or interact with subsequent processes such as liver necrosis and endothelial dysfunction. This hyperglycaemic state may, in turn, promote NF-κB-dependent transcription, inflammatory cytokine production, and oxidative stress[38–41], potentially contributing to cytokine storm or septic shock in fatal cases of EBOV disease. Therefore, the EBOV infection process and the hypothesised interactions between the virus and cellular factors may intersect with general mechanisms involved in the exacerbated inflammatory response associated with hyperglycaemia.

Hyperglycaemia can increase mitochondrial reactive oxygen species (ROS) production. Oxidative stress activates the redox-sensitive transcription factor NF-κB, which subsequently translocates to the nucleus and upregulates the expression of proinflammatory cytokines and adhesion molecules. This may establish a self-amplifying cycle of oxidative and inflammatory damage, as described, for example, in diabetic complications. Elevated intracellular glucose increases the proton gradient across the mitochondrial electron transport chain, potentially leading to an overproduction of superoxide anions, which can act as primary signalling molecules involved in pathway activation. Intracellular glucose availability is closely related to plasma glucose concentrations.

According to Claude *et al.*[42], disglycaemia is frequent among patients with fatal EBOV disease, including both hypoglycaemia and hyperglycaemia. Hyperglycaemia occurred commonly in patients with critical illness, consistent with the phenomenon of stress hyperglycaemia. In a retrospective review of 384 patients with 6,422 glucose measurements, severe hypoglycaemia (2.2 mmol/l) and hyperglycaemia (>10 mmol/l) occurred in 97 (25%) and 225 (59%) patients, respectively. Before the study by Claude *et al.*[42], the frequency, causes, and consequences of glucose disturbances in patients with EBOV disease had not been systematically examined. Greater emphasis should therefore be placed on collecting clinical data on glucose and ascorbate levels and glycaemic status in patients with EBOV disease. Dysglycaemia encompasses both hyperglycaemia and hypoglycaemia. Virus-driven hyperglycaemia could contribute to oxidative stress and increased plasma glucose concentrations by impairing cellular glucose uptake. Moreover, DHA, the oxidised form of ascorbate, and glucose can compete for GLUT1-mediated cellular uptake. Hypoglycaemia could also play an important role in EBOV pathophysiology, given the liver's central role in maintaining plasma glucose concentrations and the fact that hepatic damage and liver infection are characteristic features of EBOV disease. The pathophysiological course may therefore involve an initial virus-driven hyperglycaemia state that occurs concurrently with progressive hepatic infection. When hepatic infection and damage become clinically significant, hypoglycaemia may replace the hyperglycaemic state and contribute to a more severe pathophysiological condition. In this setting, lymphocyte apoptosis associated with inadequate glucose availability could be exacerbated, while the physiological maintenance of energy availability and plasma volume may become increasingly compromised.

Other concomitant aspects that could explain, to some extent, the pathophysiology, either alternatively or in combination with the hypothesis described above, include the preferential infection of monocytes and macrophages and the stimulation of macrophages to produce tissue factor (TF), which may contribute to cytokine storm and coagulation abnormalities. Indeed, EBOV infection can trigger severe coagulation abnormalities and bleeding complications by inducing the overexpression of procoagulant TF in monocytes and macrophages.[18]

The rapid deterioration of blood glucose levels into severe hypoglycaemia during EBOV disease could be explained by several distinct but intersecting pathways, including hepatic dysfunction resulting from necrotic liver damage and adrenal necrosis, which may reduce cortisol availability and severely compromise hepatic glucose production. Severe gastrointestinal losses can deplete glycogen reserves, cause dehydration, and impair nutrient absorption. Interestingly, another underlying mechanism could be systemic sepsis or a sepsis-like state. The hyperinflammatory response hypothesised in the present work may be associated with virus-driven oxidative stress and hyperglycaemia, and could increase peripheral glucose consumption while suppressing endogenous glucose production, driving plasma glucose concentrations to critically low levels.

No animal model studies have been designed to manipulate metabolic pathways during EBOV disease. Such studies could provide valuable insights into the pathophysiology of EBOV infection by allowing the controlled assessment of clinical parameters and providing an overall description of the pathophysiological status in relation to factors such as glucose and ascorbate levels, the extent of necrosis, direct cytolysis of the endothelium, and other relevant processes. This represents a critical, unfulfilled gap in current translational research and an opportunity to investigate the predictive potential of the present hypothesis. These processes are generally described and are relevant in many clinical conditions; their specific contribution to EBOV disease remains to be determined. The pivotal role of these phenomena in EBOV disease should therefore be the subject of further research.

According to Saad *et al.*[43], early in the disease course, haemoglobin and haematocrit levels are often elevated, sometimes before or coinciding with the onset of gastrointestinal fluid losses. As the disease progresses, anaemia commonly develops, with mean haemoglobin values below 11 g/dL reported in patients treated in Europe and the United States. As mentioned above, the viral interaction with GLUT1 or other functionally related factors such as Axl and TIM-1 could disturb the transport of glucose and ascorbate, which involves the GLUT1 transporter expressed on the erythrocyte membrane. Such

a disturbance could potentially contribute to erythrocyte and coagulation disorders. The high erythrocyte abundance could influence the distribution and availability of glucose and ascorbate in plasma. Consequently, a transient hyperglycaemic state could develop, potentially associated with activation of NF-κB-dependent transcription, inflammation, oxidative stress, and vascular damage. Hyperglycaemia induces phosphatidylserine exposure on the surfaces of erythrocytes, platelets, and endothelial cells, promoting eryptosis, a form of programmed erythrocyte cell death. In this way, according to the proposed hypothesis, EBOV GP interactions with GLUT1 or functionally related proteins linked to GLUT1 activity could represent an upstream contributor to vascular damage, haemorrhagic fever, and, ultimately, sepsis-like shock observed in fatal cases. Haemorrhages and vascular dysfunction are clinical features not only of viral haemorrhagic fevers but also of conditions such as scurvy, diabetes, thrombotic microangiopathy, and microangiopathic haemolytic anaemia.[1] The oxidised form of ascorbate (DHA) can be transported by GLUT1. Under hyperglycaemia conditions, glucose may additionally inhibit DHA uptake by cells, potentially compounding any effect of EBOV GP on cellular transport. The inability of fruit bats, primates, and humans to synthesise ascorbate from glucose may represent a vulnerability when attempting to counteract oxidative stress, particularly given limited ascorbate availability and the need to continuously support its physiological functions.

3.2. Expansion of the hypothesis to immune response and intracellular factors

In the present article, the previous hypothesis[1] is expanded by shifting the focus from membrane-level events involving viral GP and host membrane receptors to intracellular viral and cellular factors. In particular, the expanded hypothesis considers the roles of the viral proteins VP35 and VP24 in suppressing IFN responses and examines how these mechanisms may interact with pathophysiological processes involving glucose and ascorbate metabolism and the hyperglycaemic state proposed in the previous hypothesis.

The expanded hypothesis proposes that, as EBOV replication, budding, and entry into new target cells progress, the infection influences systemic physiology by disrupting glucose and ascorbate homeostasis and suppressing the IFN response through viral proteins such as VP35 and VP24. These processes may occur simultaneously and potentially reinforce one another.

Ebola virus selectively inhibits the response to IFNs, but not to IL-1β, in endothelial cells.[44] This suggests that the IFN response, along with ISG activation, may be suppressed, whereas inflammatory cytokines and NF-κB activation may remain active, potentially adding to oxidative stress and hyperglycaemia. IL-1β is a potent inducer of IL-6 production through NF-κB and STAT3-dependent signalling, and IL-6 levels are increased in patients with EBOV disease.[45]

It has been proposed that glucose and ascorbate have opposing effects on IFN responses and the CYP450 enzymatic system. Hyperglycaemia can suppress type I IFN production. In macrophages and dendritic cells, hyperglycaemia activates IRF3 and IRF7, while impairing responses to TLR3, retinoic acid-inducible gene I (RIG-I), and melanoma differentiation-associated protein 5 (MDA5). This decreases IFN-α and IFN-β production. In T-lymphocytes, hyperglycaemia can reduce differentiation towards Th1 cells and IFN-γ production, potentially promoting a shift towards inflammatory Th17 rather than antiviral phenotypes. Additionally, elevated plasma glucose concentrations can increase mitochondrial ROS production and activate protein kinase C and NF-κB, thereby contributing to oxidative stress. Hyperglycaemia may therefore exert predominantly inhibitory and dysregulatory effects on IFN signalling. It can impair JAK1 and TYK2 activity, reducing STAT1 and STAT2 phosphorylation. Advanced glycation end products formed through modification of arginine and lysine residues in key proteins may also affect IFN receptors (IFNAR1/2), STAT1, and IRF9, thereby diminishing STAT nuclear translocation. Finally, hyperglycaemia may alter the epigenetic landscape by inducing the methylation of ISG promoters, potentially reducing chromatin accessibility to STAT1 and IRF.[46,47]

Conversely, ascorbate may enhance IFN responses and regulate ISG expression. IFN signalling can generate ROS as part of the antiviral effect, whereas ascorbate may limit oxidative damage and reduce secondary inhibition of STAT1 and IRF1. This may permit a more sustained and efficient antiviral response while limiting immunopathological effects. In dendritic cells and macrophages, ascorbate can augment IRF3 and IRF7 activity and enhance responses to TLR3, TLR7/8, and RIG-I, resulting in increased secretion of IFN-α and IFN-β. In lymphocytes, it may promote differentiation into Th1 cells and increase IFN-γ production.[48–50]

Beyond the early, viral replication-associated actions of VP24 and VP35 proteins in blocking type I IFN signalling, hyperglycaemia and limited ascorbate availability could play important roles in EBOV pathophysiology, according to the novel hypothesis presented here. These metabolic factors may influence the degree of immune cell activation and the production and signalling of type I IFN (IFN-α and IFN-β) and type II IFN (IFN-γ). An important question

is whether pathways independent of VP24 and VP35 may also contribute to the inhibition of IFN signalling. While EBOV VP35 primarily antagonises type I IFN production and VP24 inhibits downstream type I IFN signalling, EBOV GP may contribute to immune evasion through distinct mechanisms. Rather than directly disrupting the canonical JAK/STAT signalling pathway, GP primarily modulates host-cell surfaces and immune-cell interactions, thereby facilitating infection and altering immune-cell function. Studies using vesicular stomatitis virus expressing EBOV GP have shown that GP alone can reproduce several aspects of EBOV interactions with immune cells and, in some contexts, can confer resistance to IFN-γ-mediated antiviral effects. However, unlike VP24/VP35, GP does not appear to directly inhibit STAT1 nuclear transport. Therefore, its contribution to IFN evasion may be distinct from, and complementary to, the mechanisms mediated by VP24 and VP35.[51–54] Several mechanisms of immune modulation by EBOV GP have been described:

- Reduced natural killer cell activation**:** EBOV GP expression on infected cells can reduce natural killer cell-mediated lysis, independently of VP24 and VP35.
- Modulation of surface receptors**:** EBOV GP can alter interactions with activating and inhibitory receptors on immune cells, such as Siglecs and selectins. GLUT1-mediated glucose transport may represent another potential mechanism linking GP-mediated cellular effects with metabolic and immune modulation.
- Cell-mediated immunity suppression**:** Although GP is not a direct antagonist of the JAK/STAT transcriptional pathway in the same manner as VP24, it can contribute to broader suppression of immune responses, including impaired dendritic cell function and reduced T-cell activation.

Ultimately, EBOV GP-mediated disruption of glucose and ascorbate homeostasis, potentially involving GLUT1-mediated transport, could represent an important component of immune modulation and metabolic dysregulation during EBOV infection.

Additionally, ascorbate may influence viral budding by modulating the redox state of specific amino acid residues in the VP40 matrix protein. Cys311 and Cys314 residues (cysteine residues 311 and 314) are located in the C-terminal domain of VP40 and have been proposed to function as sensors of the cellular redox state. The redox state of these residues may influence viral budding. Under oxidising conditions, these cysteine residues can form a disulfide bond, potentially restricting the conformational flexibility of VP40. This CX_nC motif may also be subject to post-translational modifications, including S-nitrosylation and S-glutathionylation. Ascorbate can promote a more reducing intracellular environment; reduction of the disulfide bond may therefore alter VP40 interactions with phosphatidylserine and affect the morphology and efficiency of viral particle formation. In this context, ascorbate-dependent regulation of the intracellular redox state could influence the redox state of VP40 and, consequently, the viral budding process.[55–57]

For its part, hyperglycaemia (25–50 mM) has been shown to cause a dose-dependent increase in phosphatidylserine exposure on the surface of human erythrocytes. This effect is mediated by increased activity and membrane expression of the Ca^{2+}-dependent phospholipid scramblase 1, driven by dysregulated calcium homeostasis and oxidative stress.[58,59] Increased phosphatidylserine exposure could potentially contribute to viral dissemination and cellular entry through apoptotic mimicry, a mechanism EBOV uses to facilitate interactions with host cells.

Ebola virus infection also profoundly affects hepatic physiology and is associated with a general reduction in the expression of genes involved in hepatic function. EBOV infection also significantly disrupts the hepatic CYP450 enzymatic system, thereby reducing the liver's metabolic capacity. Within the liver, ascorbate and glucose may exert opposing effects on oxidative stress and, consequently, on the stability and activity of CYP450 phase I enzymes. Ascorbate can protect CYP450 enzymes against oxidative damage[60], whereas elevated glucose levels can impair CYP450 activity, potentially by altering the hepatic lipid environment. Experiments using CYP2E1-overexpressing cells further illustrate the critical relationship between ROS, antioxidant defences and oxidative cellular injury. When levels of the key cellular antioxidant reduced glutathione (GSH) were lowered by inhibiting GSH synthesis with buthionine sulfoximine, arachidonic acid-induced toxicity was enhanced. Conversely, supplementation with various antioxidants conferred protection. GSH and ascorbate function synergistically in the ascorbate–GSH cycle to neutralise ROS and maintain cellular redox balance. GSH-dependent reducing systems can facilitate regeneration of ascorbate from DHA, thereby sustaining cellular antioxidant capacity. Ascorbate may also protect CYP2E1 from oxidative inactivation caused by ROS generated during the CYP450 catalytic cycle. Furthermore, ascorbate can promote the reduction of Fe^{3+} to Fe^{2+} in CYP3A4, potentially supporting its catalytic activity.[60]

Regarding the signalling pathways involved in viral entry and virus–cell interactions, the PI3K/Akt pathway plays an important role in EBOV cellular entry.[61] EBOV triggers receptor tyrosine kinase-dependent signalling through receptors such as epidermal growth factor receptor (EGFR), c-Met, and TAM receptors, including

Axl, to facilitate the uptake and intracellular trafficking of viral particles.[62] These kinases activate essential downstream pathways, including PI3K/Akt, and modulate macropinocytosis, thereby facilitating delivery of viral particles to intracellular compartments containing the NPC1 receptor. EGFR signalling can also increase glucose uptake and lactate production through PI3K/Akt-dependent pathways. Consistent with this mechanism, EBOV induces PI3K activity, whereas inhibition of PI3K, Akt, or Rac1 disrupts the normal uptake of virus particles into cells. Within the central hypothesis proposed here, which focuses on glucose and ascorbate homeostasis, the redox sensitivity of the PI3K/Akt pathway provides a potential mechanistic link between cellular metabolism and EBOV entry. Ascorbate can modulate intracellular redox status, which may influence PI3K/Akt signalling. In turn, PI3K/Akt signalling promotes GLUT1 expression and facilitates GLUT1 translocation to the plasma membrane.[63] Therefore, EBOV-induced activation of PI3K/Akt and GLUT1-mediated glucose transport may be functionally interconnected. Available functional GLUT1 may also increase cellular DHA uptake, thereby linking glucose and ascorbate metabolism to intracellular redox regulation. Increased DHA uptake and its subsequent reduction to ascorbate could influence cellular redox status and immune responses and may, in the proposed model, attenuate excessive PI3K/Akt activation associated with oxidative stress. Mechanistically, ROS can activate PI3K/Akt signalling, in part by oxidatively inhibiting protein phosphatases that normally antagonise the pathway. By reducing oxidative stress, ascorbate could therefore favour the activity of phosphatases such as phosphatase and tensin homolog, an important negative regulator of PI3K signalling. These interactions suggest a potential feedback relationship between EBOV-induced PI3K/Akt activation, GLUT1-mediated glucose and DHA transport, and intracellular redox homeostasis.

Other haemorrhagic fever viruses such as Lassa fever virus (LASV) and dengue virus may also disrupt glucose and ascorbate homeostasis.[1] Both viruses can interact with TIM-1 and Axl during cellular entry, raising the possibility that these receptor-mediated processes may be functionally linked to GLUT1-dependent metabolic pathways. However, this proposed relationship remains to be experimentally established and warrants further investigation.

Dengue and Lassa viruses incorporate phosphatidylserine into their envelopes and can interact with TIM-1 and Axl during entry, although the mechanisms and relative importance of these receptors differ between viruses.[1] Because phosphatidylserine-mediated apoptotic mimicry represents a broadly utilised mechanism of viral entry, it is conceivable that metabolic disturbances associated with hyperglycaemia could influence this process not only for filoviruses, but also in other viral haemorrhagic fevers.

The exonuclease domain of the LASV nucleoprotein (ExoN) is a major antagonist of the host IFN response. It functions as a 3'–5' exonuclease that degrades double-stranded RNA, reducing the availability of viral RNA to host innate immune sensors such as RIG-I. The LASV Z protein further suppresses the innate immune response through interactions with the caspase activation and recruitment domains of RIG-I and MDA5, thereby interfering with downstream signalling.[64,65] ExoN activity is also essential for efficient viral replication. Within the hypothesis proposed here, ascorbate and hyperglycaemia could potentially influence these IFN-antagonistic mechanisms through their effects on intracellular redox balance, oxidative stress and metal-ion homeostasis. The catalytic activity of LASV ExoN depends on divalent metal ions and involves a two-metal-ion catalytic mechanism using manganese or magnesium. Zinc (Zn) binding may also contribute to the structural stability of the protein domain. Because cysteine residues involved in Zn coordination can be sensitive to changes in the cellular redox environment, alterations in intracellular redox status could potentially influence the structural integrity or activity of Zn-dependent viral proteins. The structural importance of Zn-coordinating domains is well established in other biological systems. As described by Padjasek *et al.*[66], analysis of the *Xenopus laevis* TFIIIA sequence showed that amino acid residues from 13 to 276 form a continuous run of nine tandemly repeated 30 amino acid residues, each containing two invariant pairs of Cys and His residues coordinating one Zn(II), subsequently recognised as zinc fingers (ZFs). Subsequent studies established that besides the fundamental Cys and His residues, there are several other conserved hydrophobic amino acid residues, i.e., Tyr2 (Phe2, Leu2), Phe11 and Leu17, that are likely to form a structural hydrophobic core in the folded structure. However, these hydrophobic residues can be different depending on the ZFs sequence. In other words, each ZF motif consists of seven conserved amino acid residues that provide a framework for tertiary folding, while some of the variable residues determine the specificity of each domain.

LASV ExoN activity is dependent on divalent cations.[67–69] Cellular transport and distribution of these ions involve members of the ZIP (SLC39) and ZnT (SLC30) transporter families. ZIP14 (SLC39A14), in particular, is responsive to inflammatory conditions and has been associated with increased expression of IL-6 and nitric oxide. Aydemir and Cousins[70] reported that ZIP14 expression was IL-6-dependent and that treatment of mice with IL-1β increased

ZIP14 expression and Zn uptake. Accordingly, ascorbate's effects on intracellular redox status, oxidative stress, and inflammation could influence the availability and distribution of divalent cations and thereby affect metal-dependent viral proteins such as LASV ExoN. In this context, reduced oxidative and inflammatory signalling could alter ZIP14-mediated metal-ion homeostasis and, consequently, the cellular environment required for ExoN activity.

4. Conclusion

If this hypothesis holds, supportive care for EBOVHF could be improved by targeting metabolic pathways that contribute to its pathophysiology. A potential therapeutic strategy could involve careful regulation of blood glucose concentrations, using glucose or insulin as clinically appropriate to maintain physiological glucose homeostasis, together with adequate ascorbate and GSH supplementation to counteract oxidative stress and support cellular antioxidant defences. Intracellular reducing systems, including GSH-dependent pathways, contribute to the regeneration of ascorbate from DHA. Maintaining adequate ascorbate availability could potentially mitigate oxidative and inflammatory stress and thereby reduce the risk of severe vascular dysfunction, shock and multiorgan injury. Within the proposed framework, maintenance of ascorbate availability could also influence immune function by supporting lymphocyte responses, modulating cytokine storm, and potentially enhancing adaptive immune responses and IFN-mediated antiviral activity. Furthermore, ascorbate may influence viral budding and, consequently, viral dissemination, as discussed above. These potential effects provide a rationale for investigating whether restoration of glucose and ascorbate homeostasis could complement established supportive measures in patients with EBOV disease.

The proposed therapeutic concept is hypothetical and should not be interpreted as an established clinical treatment. Its primary purpose is to provide a mechanistic framework for generating experimentally testable hypotheses. Specifically, translational and clinical research is warranted to determine whether modulating glucose homeostasis and supplementing with ascorbate and GSH can influence viral replication, immune dysfunction, oxidative stress, vascular injury and clinical outcomes in EBOV disease. Such studies should also establish the appropriate doses, timing, safety and potential interactions of these interventions with standard supportive and antiviral therapies.

5. Future perspectives

The proposed interactions between the viral GP and GLUT1 in EBOV and other haemorrhagic fever-causing viruses should be investigated experimentally, together with the other predictions and assumptions arising from this analysis. Clinical data on ascorbate administration and the maintenance of physiological plasma glucose levels in patients, particularly in relation to disease progression and clinical outcomes, would be of considerable interest. These clinical observations should be complemented by experimental studies investigating the molecular mechanisms underlying the proposed pathophysiological processes.

As research into virus–host interactions progresses, it may eventually become possible to classify viruses according to the key metabolic pathways they perturb and host factors they engage. Such a framework could provide a broader perspective on the relationship between viral pathogenesis, host metabolism and disease severity, and may help identify novel metabolic targets for therapeutic intervention.

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The author declares no conflict of interest.

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