

A Hypothesis Expanded: Role of Ascorbate and Glucose in the Pathophysiology of Ebola Haemorrhagic Fever Considering Intracellular Factors and Viral Proteins Apart from the Envelope Glycoprotein

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Hypothesis

A Hypothesis Expanded: Role of Ascorbate and Glucose in the Pathophysiology of Ebola Haemorrhagic Fever Considering Intracellular Factors and Viral Proteins Apart from the Envelope Glycoprotein

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Abstract

Glucose and ascorbate transport and their opposite effects on the physiological processes, explain the pathophysiology of the Ebola virus. The virus impairs intracellularly the interferon (IFN) signalling. The present article will focus on the viral factors (VP24, VP35, VP40 proteins, nucleoprotein NP) that operate in the inner of the cell, subsequently to the viral entry. The haemorrhagic fever syndrome could be understood as a state of oxidative stress, driven by hyperglycaemia and the activation of NF- κ B pathway and inflammatory cytokines. High glucose levels in plasma contributes to oxidative stress. It has also an inhibitory effect on Interferon (IFN) signalling. Conversely, ascorbate can counteract the IFN blocking exerted by the virus and interfere virus budding. A treatment strategy would focus on the administration of ascorbate and glutathione, glucose or insulin at convenience, in order to maintain constant and normal levels of glucose in plasma, to combat the oxidative and inflammatory stress.

Keywords: Ebola virus; Glut-1; ascorbate; glucose; VP24; VP40; interferon; NF- κ B; oxidative stress; IL-6; CYP450; Lassa Fever virus

1. Introduction

Regarding Ebola virus infection, there doesn't used to be a comprehensive biological explanation of the violence and systemic character of the illness manifestations and of the pathophysiology. Many experimental data are available nowadays, that have rendered important descriptive and molecular information, and have rendered as well the approach to key factors. In a previous opinion article published by the same author in F1000 Research, it was discussed the pathophysiological process in haemorrhagic fever causing viruses (mainly Filoviruses), focusing on the virus entry process and the interaction of the viral glycoprotein of the virion envelope with host factors [1]. In that former article it was explained the hypothesis of a pivotal role of glucose and ascorbate in the pathophysiological changes during infection, involving glucose and ascorbate homeostasis deregulation and a subsequent oxidative stress, the activation of NF- κ B pathway and a cytokine storm causing multiple tissue damage.

The present article, complementary to the previously published, will focus on the viral factors (VP24, VP40 proteins, nucleoprotein, NP) that operate in the internal compartments of the cell, subsequently to the viral entry. Pathological and molecular processes like the interferon-suppression activity exerted by the virus or the interplay between the virus and the immune system would be discussed, in connection with other pathophysiological regulatory systems, like the role of the enzymatic system CYP450 in hepatocytes in the liver and its interplay with liver damage caused by the virus and the suppression of the interferon (IFN) response. It would be analysed the role of

glucose and ascorbate in the immune response, the redox state in the cell and its influence in the viral activity or the interplay between the virus, the homeostasis and the haemorrhagic fever syndrome as a state of oxidative stress, driven by hyperglycaemia and the activation of the NF- κ B pathway and inflammatory cytokines.

1.1. The Ebola Virus (EBOV)

As described in two reference general Virology books [2,3], *Molekulare Virologie*, written in German by Susanne Modrow and colleagues, and *The Field's Virology* (Peter M. Howley and David M. Knipe as editors in-chief) the family of Filoviridae belongs, like other viruses like Rhabdo-, Borna-Pneumo- and Paramyxoviridae, to the Order Mononegavirales. The virions have an irregular, *pleomorphic* form. The filaments can be branched, have a U-form or are folded as a spiral. The particles have a constant diameter of 80nm, the length is highly variable (up to 14.000 nm). The Marburg virus (MARV) presents generally 665nm in length, and Ebola virus (EBOV) throws a value of 805 nm.

The filaments are constituted of a helical nucleocapsid. It is made up of RNA genome and the filovirus ribonucleoprotein (RNP) complex components: nucleoprotein (NP), polymerase cofactor VP35, transcriptional activator VP30, large protein L (RNA-dependent RNA polymerase) and RNP complex-associated protein VP24. VP30 is described as minor nucleoprotein, and regulates the replication and transcription. The nucleocapsid is wrapped in a viral envelope. The matrix proteins VP40 (major) and VP24(minor) are associated with the inner layer of the lipid envelope and the protein-consisting parts of the nucleocapsid. In the viral envelope are embedded the viral glycoproteins (GP) that exist as a trimer, and project approximately 7 nm from the surface of the virus. The viral glycoprotein GP is embedded in the envelope and is exposed as the only viral component of the surface. GP is highly modified by carbohydrate groups, which are linked to aminoacidic residues by N- and O- glycosidic bonds. As type-I membrane proteins, the GP proteins are associated through a hydrophobic aminoacidic segment at the carboxyl end, with the virus and the cytoplasm membrane of the infected cell. The GP proteins consist of two subunits: GP1 and GP2 and are responsible for the interaction of the virions with the target cells (GP1) and the fusion of the viral envelope with the endosome membrane of the cell.

The EBOV glycoprotein (GP) mediates virus entry [4–6]. The cellular factors described as mediators for virus entry are:

- Universal mammalian filovirus receptor: Niemann Pick receptor of the endosomal compartment (NPC1). This protein is required for filovirus entry and confers susceptibility to filovirus infection when expressed in non-permissive reptilian cells.[7]
- Attachment factors:
- TAM receptor Axl has been proven to enhance Ebola virus particles micropinocytosis [8].
- TIM-1, T-cell Ig and mucin domain 1 (also known as hepatitis A virus cellular receptor 1 (HAVCR1)) binds to the receptor binding domain of the Zaire EBOV glucoprotein, and ectopic TIM-1 expression in poorly permissive cells enhances EBOV infection by 10- to 30-fold [9].

Subsequent to attachment, filoviruses enter host cells by endocytosis, generally, but likely not exclusively, micropinocytosis. In the low pH environment of the endolysosome, the GP1 subunit is cleaved by cathepsins B and L, thereby releasing the mucin-like subdomains and glycan caps to expose the receptor-binding site [3]. Once exposed, the GP1 receptor-binding site engages the domain C of NPC1.

TIM-1, as indicated, binds directly to EBOV-GP, but its principal function is to bind to phosphatidylserine residues in apoptotic cells through its IgV domain. Axl binds to Gas6 (Growth Arrest-Specific 6) which, in turn, binds to phosphatidylserine. As mentioned in the previous presentation of the hypothesis [1], EBOV incorporates phosphatidylserine in its envelope, tying to trick the target cell into phagocytosing the virus (apoptotic mimicry). In the process of budding, by action of the VP40 matrix protein, the virus hijacks scramblases Xkr8 and TMEM16F to incorporate phosphatidylserine in the envelope. The correct budding of the viral particles depends on the presence of functional phosphatidylserine, which is clustered by VP40 in the site of budding [10,11].

The four structural proteins -nucleoprotein (NP), RNA-dependent RNA polymerase, VP30 and VP35 are important for viral genome amplification [12]. EBOV VP40 is essential for viral budding [13]. As described in the article by Kuroda et al. [14], EBOV VP24 and VP35 are key components of the nucleocapsid, with VP24 facilitating correct nucleocapsid assembly. The activation of INF and IFN during EBOV infection can be counteracted by VP35, which inhibits the phosphorylation and subsequent nuclear translocation of interferon regulatory factor 3 (IRF3) [15]. When interferon IFN is released from infected cells it binds to IFN receptors on neighboring cells, resulting in the activation of JAK/STAT-dependent signalling pathways. This activation can be counteracted by VP24 through the inhibition of STAT-1 nuclear translocation. Activation of JAK/STAT pathways leads to the induction of interferon-stimulated genes (ISGs), whose products may directly limit viral replication. However, once again, EBOV has evolved countermeasures against the action of ISGs; for example, VP35 blocks PKR activation [16] and GP blocks BST2/ tetherin-mediated restriction of viral budding [17]. Budding filovirions not only contain part of the plasma membrane (including phosphatidylserine), but also the membrane-incorporated GP_{1,2} as progeny peplomers. Phosphatidylserine, the substrate for filovirion attachment factors such as TIM-1, is flipped from the inner leaflet of the plasma membrane to the outer leaflet of the filovirion envelope by cellular scramblases [3].

1.2. Pathology of the Ebola Virus Haemorrhagic Fever (EBOVHF)

According to literature major symptoms of Ebola virus disease include a maculopapular rash and mucosal haemorrhage. It begins unspecific with fever, asthenia, diarrhoea, headaches, myalgia, arthralgia, vomiting and abdominal pain and disease course develops sharply and resolves in survival or death in the course of approximately 3 weeks. Massive bleeding along with fluid distribution problems, disseminated intravascular coagulation and focal necrosis are observed in fatal cases. Arthralgia, asthenia, and neurological disorders, as dysesthesias, are often sequelae in the convalescence, which lasts weeks to months. Main features of Ebola virus haemorrhagic fevers can be consulted in available literature [18–21].

The Ebola virus has a broad cellular tropism, and infects cells of a variety of cell types and tissues. It is well established that, in the early phase of infection the virus targets dendritic cells, monocytes and activated macrophages and possibly endothelial cells, although Endothelial damage during filovirus infection with no evidence of direct endothelial cytolysis has previously been described, suggesting the idea that other indirect mechanisms governing vasculature injury are present [22]. The pathohistological studies reveal frequent necrosis in the liver, spleen and lymph nodes [23]. In the late state of the illness occur fluid distribution problems, multiple and widespread haemorrhages, and multi-organ failure. The overall symptoms and pathophysiological process resemble the septic shock [21]. Patients with fatal filovirus infection die with very high viremia, an absence of mononuclear phagocytic infiltration into sites of infection and little evidence of a humoral or T-cell mediated response [24]. In addition, filoviruses are resistant to the effects of the antiviral properties of interferon (IFN).

1.3. Interferons (IFNs) and the Immune System: The Pivotal Role of Interferons (IFNs) and Interferon-Induced Antiviral Response

Interferons (IFNs) are critical signalling proteins (a type of cytokines) that act as the immune system's main line of defence against pathogens, particularly viruses, by activating antiviral, antiproliferative and immunomodulatory pathways. IFNs are classified into three main types: I, II and III, based on receptor usage and cell origin. Type I IFNs are INF- α , INF- β , INF- ϵ , INF- κ and INF- ω . Are produced by nearly all nucleated cells, including dendritic cells, upon viral recognition. They induce an antiviral state in surrounding cells by degrading viral RNA and inhibiting protein synthesis. Type-I IFNs increase also the expression of the major histocompatibility complex class I (MHC-I). INF- γ represents the type -II IFNs, and is produced by activated T-cells and natural killer cells (NK cells). Is a key activator of macrophages, enhancing their ability to kill pathogens and tumor

cells. It boosts MHC class II expression, and bridges innate and adaptive immunity, inducing inflammation. $\text{INF-}\gamma$ exerts several metabolic influences, modulating glucose metabolism at both the systemic and cellular levels to ensure optimal immune responses while restricting viral replication [25,26]. The type III IFNs are represented by the $\text{INF-}\lambda$ family, and are produced early in infection, similar to type I, but primarily at epithelial barriers, with a more limited receptor expression.

The interferon regulatory factor 3 (IRF3) is activated through specific signalling pathways, most notably the cGAS-STING axis, RIG-I like receptors (RLRs) and Toll-like receptors 3 and 4 (TLR3/4), which detect viral nucleic acids. In the nucleus IRF3 acts with NF- κ B and AP-1 to form an *enhanceosome* on the promoters of several target genes, resulting in driving the expression of type I and type III IFNs. IFNs induce the activation of JAK/STAT-dependent signalling pathways. As mentioned, activation of JAK/STAT pathways leads to the induction of interferon-stimulated genes (ISGs). $\text{INF-}\alpha$, $\text{INF-}\beta$, and $\text{INF-}\omega$ utilize a common receptor (IFNAR) to activate JAK1 and Tyk2, leading to the activation of STAT1 and STAT2. $\text{INF-}\gamma$ signals through the $\text{INF-}\gamma$ receptor to activate JAK1 and JAK2, which predominantly phosphorylate STAT1.

TLR3 and TLR4 are immune innate receptors that are essential for bridging innate and adaptive immunity. They are involved in the detection of pathogens and trigger immune responses and the release of inflammatory cytokines. TLR3 is localized in the endosomal membrane and TLR4 is expressed on the surface of the cells, such as macrophages, neutrophils and dendritic cells. TLR3 functions through the TRIF-dependent pathway to produce type-I IFNs. TLR4 exhibits a dual signalling mechanism: at the plasma membrane it activates NF- κ B pathway. When endocytosed, it triggers the TRIF adapter pathway, leading to type-I IFN production.

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

Interleukin 1-(IL-1) is a proinflammatory cytokine critical for immune activation and metabolic reprogramming [25,28] Produced in response to pathogen- or damage associated molecular patterns (PAMPs and DAMPs, IL 1- is regulated via nuclear factor kappa beta (NF- κ B) signalling and inflammasome mediated caspase-1 cleavage. Upon binding to its receptor, activates MAPK and PI3K/Akt pathways, promoting glycolysis in immune cells. This involves upregulation of Glut-1 and glycolytic enzymes.

IL-6 is another pro-inflammatory cytokine with significant effects on glucose metabolism (25, 29). It enhances hepatic gluconeogenesis, by activating the Janus kinase transducer and activator of transcription 3 (JAK-STAT3) pathway in hepatocytes, resulting in the increased expression of gluconeogenic enzymes, contributing to hyperglycaemia, which is mostly observed in severe viral infections and cytokine storm syndromes [25,29,30].

1.4. Cytochrome P450 Enzymatic System (CYP450) in Hepatocytes: The Chemical Defence and Its Relation with the Immune System. Defence

According to Coutiño Rodriguez et al., [31] CYP-450 takes part in defending organisms from stressing chemical conditions, in response to different xenobiotics (XbS). It has a critical influence on the metabolic regulation of the organism as a whole. From the perspective of its regulation by nuclear receptors, is associated and related to the immune system. Both represent a system and mechanism to biologically and chemically recognize the self and non-self, structures. Indeed, there is a high degree of homology between the cytochrome superfamily, specially CYP450 2D6, CYP450 2D9 and the kappa chain of the γ -immunoglobulin (IG-G).

CYP450 enzymes are monooxygenases that introduce a single oxygen atom into a substrate (RH) while reducing the second oxygen atom of O_2 to water. One atom forms water, while the other is inserted into the substrate, forming a hydroxylated product (ROH). The oxidized substrate is then released and a re-oxidation process occurs: the enzyme returns to its original oxidized Ferric (Fe^{3+}) state.

The levels of inflammatory cytokines can decrease the activity of several CYP450 isoforms. On the other hand, it has been found that CYP1 inhibition increased the expression levels of the stem cell factor receptor (c-Kit) and interleukin (IL)-22 but decreased IL-17. Single cell analyses showed that CYP1 inhibition especially promoted CD4⁺ helper T (Th) cells that co-express c-Kit and IL-22 simultaneously [32].

2. Discussion of the Literature-Based Evidence: The Hypothesis Expanded

The previously hypothesis presented in a previous article by this author, analyses the evidence supporting a pivotal role of glucose and ascorbate homeostasis in EBOV disease [1]. Interestingly, expression of Glut-1, glucose and dehydroascorbate (DHA) transporter 1 on the erythrocyte membrane is associated with the inability to synthesize ascorbate and is restricted to that very species that are susceptible to filoviruses or are considered to be the reservoir of the virus in nature (primates, humans and fruit bats). There is some sequence homology [1] between the EBOV glycoprotein (GP) and the GP of HTLV-I, a retrovirus that uses Glut-1 as a receptor for virus entry. By the interaction or binding of the EBOV GP to Glut-1 or other functionally related proteins that also act as EBOV attachment factors or receptors (Axl TAM receptor and TIM-1), which on their own could be related to glucose metabolism, EBOV could disturb the availability of glucose and ascorbate for the cells, especially in lymphocytes and other immune cells that have highly glycolytic demands (Warburg effect) [33,34]. In EBOV disease apoptosis of lymphocytes is a relevant clinical feature: the poor availability of glucose and ascorbate for lymphocytes, by means of the viral GP-Glut-1 interactions (additionally, other related cell factors can be considered) could be the cause of the observed apoptosis of lymphocytes, at least one important reason. The result of EBOV GP interactions with host factors would be, in the end, a hyperglycaemic state: high levels of glucose in plasma, low levels of ascorbate in the cells and impaired glucose transport. This hyperglycaemic state, in turn, promotes NF- κ B transcription, inflammatory cytokine production and oxidative stress [35–38], that leads to cytokine storming or septic shock in the Ebola virus disease fatal cases. According to Kasereka Masumbuko Claude and colleagues [39], in fatal Ebola virus patients disglycaemia is frequent: hypoglycaemia and hyperglycaemia. Hyperglycaemia occurred commonly in patients with critical illness (which is known as stress hyperglycaemia). In a retrospective review of periods of 384 patients with 6422 glucose measurements, severe hypoglycaemia (2.2mmol/l) and hyperglycaemia ($\geq 10\text{mmol/l}$) occurred in 97 (25%) and 225 (59%) patients, respectively.

Once again, as mentioned, the viral interaction with Glut-1 or other functionally related factor (Axl, TIM-1) according to the hypothesis, can disturb the transport of glucose and ascorbate, which involves primarily the Glut-1 transporter present in the erythrocyte membrane. It could be cause of erythrocyte and coagulation disorders. The high erythrocyte numbers result in their control of the levels of glucose and ascorbate in plasma. As a consequence, a transient hyperglycaemia would be established, which is associated with the activation of NF- κ B transcription, inflammation, oxidative stress and the associated vascular damage. Hyperglycaemia induces phosphatidylserine (PS) exposure on the surface of erythrocytes, platelets and endothelial cells, promoting eryptosis, a suicidal cell death process. This way, EBOV GP interaction with Glut-1 or functionally related proteins, linked to Glut-1 activity, would be the primary origin of the vascular damage, haemorrhagic fever and, ultimately, septic shock in fatal cases. Haemorrhages and vasculature dysfunctions are a clinical feature not only of viral haemorrhagic fevers, but also in scurvy, diabetes and thrombotic, microangiopathic haemolytic anaemia [1]. The oxidized form of ascorbate (dehydroascorbate, DHA) shares the same transporter Glut-1. In hyperglycaemia conditions, the glucose can inhibit, additionally to the EBOV GP itself, the DHA uptake by the cells. The inability of fruit bats, primates and humans to synthesize ascorbate from glucose is an Achille's heel when trying to counteract the effects of oxidative stress and the lack of ascorbate pools to provide continuous support of its physiological functions.

In the present article, it would be expanded that prior hypothesis [1], focusing in the role of cellular and viral factors that act beyond the cytoplasmic membrane, viral glycoproteins and

membrane receptors: for example, the role of VP35 and VP24 viral proteins in blocking the interferon response, and the relation of this process and other pathophysiological mechanisms with the glucose and ascorbate metabolism and the central hyperglycaemic state which was primarily hypothesized:

As considered previously, as EBOV replication, budding and entry into new target cells progress, it influences systemic physiology, disturbing glucose and ascorbate homeostasis and blocking IFN response by means of the initial action of viral proteins VP35 and VP24. Both processes occur simultaneously.

It has been shown that EBOV selectively inhibits response to Interferons (IFNs) but not Interleukin-1 β , in endothelial cells [40]. It means that IFN response would be blocked, as well as the activation of Interferon Stimulated genes (ISGs), but the adverse effects of inflammatory cytokine concentration and NF- κ B transcription could not be avoided, adding to the effects of oxidative stress and hyperglycaemia. IL-1 β is a potent inducer of the production of IL-6, through NF- κ B and STAT3 signalling. IL-6 levels are increased in EBOV disease patients [41].

Glucose and ascorbate have opposite effects on INF responses and the CYP450 enzymatic system. Hyperglycaemia suppresses the production of type I IFN. In macrophages and dendritic cells (DCs) hyperglycaemia activates Interferon regulatory factors IRF3 and IRF7, inducing a poor response to Toll-like Receptor 3 (TLR3), RIG-I and MDAS. It results in the decrease of IFN- α and IFN- β production. In T-lymphocytes, hyperglycaemia decreases the differentiation into Th1-type cells and the production of IF- γ . It produces a shift towards inflammatory Th17/not antiviral phenotypes. Additionally, high glucose levels in plasma augment the production of mitochondrial *reactive oxygen species* (ROS), and induce the activation of PKC and NF-B transcription, contributing to oxidative stress. Hyperglycaemia has a mainly inhibitory and deregulatory effect on IFN signalling. It produces the functional inhibition of Janus kinase transducer and activator of transcription 1 (JAK1) and TYK2, and a decrease in STAT1 and STAT2 phosphorylation. The advanced glycation of end products in arginine and lysine residues in key proteins affect IFN receptors (IFNAR1/2, STAT1 and IRF9, diminishing the STAT nuclear translocation. Finally, hyperglycaemia affects the epigenetic picture, and induces the methylation of Interferon-stimulated genes promoters (ISGs-promoters), and chromatin is less accessible to STAT1 and Interferon regulatory factors (IRF) [42,43].

Conversely, ascorbate activates Interferon (IFNs) and regulates ISGs. IFN generates ROS inherently to its antiviral effect. Ascorbate limits the oxidative damage and avoids the secondary inhibition of STAT1 and IRF1. It permits a long-lasting, efficient antiviral response without immunopathological effects. In DCs and macrophages, ascorbate augments the activity of IRF3 and IRF7 and improves the response to TLR3, TLR7/8 and RIG-I, resulting in the secretion of more IFN- α and IFN- β . In lymphocytes it promotes the differentiation into Th1 cells and the production of IFN- γ [44–46].

Apart from the initial and the viral replication-associated action of VP24 and VP35 proteins blocking IFN-I signalling, hyperglycaemia and lack of ascorbate availability could play a role, as main players of EBOV pathophysiology, as factors governing the increase or the decrease of activation of immune cells and IFN-I (INF- α AND IFN- β) and IFN-II (IFN- γ). Could there be an VP-24 and VP35-independent pathway to block interferon signalling? While EBOV VP35 blocks IFN-I production and VP24 inhibits signalling, there is indeed a GP-mediated mechanism primarily involving modulating host immune cell surfaces and facilitating infection of immune cells, rather than directly disrupting the canonical JAK/STAT signalling pathway. In studies using VSV-EBOV-GP, the glycoprotein is sufficient to mimic aspects of the Ebola virus infection in terms of immune cell interaction and, in some contexts, shows resistance to interferon-gamma mediated antiviral effects. However, unlike VP24/VP35, the glycoprotein does not act as a direct inhibitor of STAT1 nuclear transport, making its contribution to IFN evasion distinct and complementary to VP24 and VP35. [47–50]. Some describe mechanisms of immune modulation by EBOV-GP are:

- Reduced NK cells activation: EBOV-GP expression on infected cells reduces natural killer (NK) cell-mediated lysis, acting independently of VP24/VP35.

- Modulation of surface receptors: EBOV-GP has been shown to modulate the interactions with activating and inhibitory receptors, such as Siglecs and selectins, on immune cells. Glut-1 could be other candidate.
- Cell-mediated immunity suppression: Although GP is not a direct antagonist of the JAK/STAT transcription pathway like VP24, it contributes to a global downregulation of immune responses in dendritic cells and the suppression of T-cell activation.

Ultimately, the EBOV-GP-mediated disruption of the glucose and ascorbate homeostasis and Glut-1-mediated transport, could be a key in the immune modulation and disruption.

Additionally, ascorbate can even have an incidence on the process of viral budding, controlling the redox state of certain aminoacidic residues of the VP40 matrix protein. The Cys311 and Cys314 residues (Cysteine residues 311,314) are located in the C-terminal domain of the matrix protein VP40 and function as a sensor of the redox state. The redox state of these residues is critical for budding: in oxidic conditions, these cysteines can form a disulfide bond, restringing the flexibility. This CX_nC motif is a target of post-translational modifications, as are S-nitrosylation and S-glutathionylation. Ascorbate can modify the redox state into more reducing conditions, so that the reduction of the disulfide bond results in more affinity for the phosphatidylserine and in distorted, more long, aberrant viral particles. Ascorbate controls the redox state of the inner cell so that it can interfere with the budding process [51–53].

For its part, hyperglycaemia (25-50mM) leads to 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 Ca²⁺-dependent PLSCR1 scramblase, driven by dysregulated calcium homeostasis and oxidative stress [54,55]. This would add to the virus dissemination and entry into the cells, given that EBOV uses apoptotic mimicry.

On the other hand, the EBOV infection affects profoundly the liver physiology, and produces a generalized decrease in the gene expression of the hepatic function. EBOV infection disturbs significantly the cytochrome P450 enzymatic system (CYP450) in the liver, reducing its metabolic capacity. In the liver ascorbate and glucose act in opposite directions, in relation to the oxidative stress, affecting the stability of the CYP450 phase I enzymes. Ascorbate usually protects CYP450 function against oxidative damage [56], whereas glucose decreases the CYP450 activity, altering the lipidic environment in the liver. Experiments with CYP2E1-overexpressing cells illustrate the critical relationship between ROS and antioxidants in production of oxidative stress and resultant cell injury. Thus, when levels of the key cellular antioxidant, reduced glutathione (GSH), were lowered by inhibiting GSH synthesis with buthionine sulfoximine (BSO), arachidonic acid toxicity was enhanced. Conversely, supplementing cellular defences with a range of antioxidants, conferred protection. GSH and ascorbate are antioxidants that work synergistically in the ascorbate-glutathione cycle to neutralize reactive oxygen species (ROS) and maintain cellular redox balance. GSH regenerates oxidized ascorbate (dehydroascorbate, DHA), which in turn acts as a crucial scavenger. Ascorbate also protects CYP2E1 from the oxidative inactivation by the reactive oxygen species (ROS), that these CYP450 enzymes release during their catalytic cycle. Ascorbate can stimulate the reduction of Fe³⁺ to Fe²⁺ in CYP450A4, promoting its catalytic activity [56].

In relation to the signalling pathways involved in entry and virus-cell interactions, Phosphoinositide-3 kinase-Akt pathway (PI3K/Akt) controls cellular entry of EBOV [57]. Ebola virus (EBOV) triggers Receptor Tyrosine Kinase (RTK)-dependent signaling, including Epidermal growth factor receptor (EGFR), c-Met, and TAM receptors (Axl), to facilitate the delivery of viral particles into host cells [58]. These kinases activate essential downstream pathways like PI3K/Akt and modulate macropinocytosis, ensuring the virus reaches necessary intracellular compartments containing the NPC1 receptor. EGFR signalling increases glucose uptake and lactate production via PI3K/Akt-dependent pathways. EBOV induces PI3K activity, and inhibitors of PI3K, Akt, or Rac1 disrupt the normal uptake of virus particles into cells. Once again, and focusing on the central point of the hypothesis, which is the glucose and ascorbate homeostasis, ascorbate modulates the redox state of PI3K/Akt, which is redox-sensitive. PI3K/Akt increases the Glut-1 expression and promotes

the Glut-1 localization in the cytoplasmatic membrane [59]. The availability of functional Glut-1 increases the influx of DHA (dehydroascorbate), which, in turn, modulates the redox state, influences the immune responses, and reduces the hyperactivation of PI3K, induced by oxidative stress. In detail, ascorbate reduces ROS (reactive oxygen species); ROS normally activate PI3K/Akt by inhibiting phosphatases. When ascorbate reduces ROS, it favours also the activity of PTEN, an important PI3K antagonist.

Other haemorrhagic fever-causing viruses, like Lassa fever virus (LASV) and Dengue Virus (DENV), are also supposed to cause a pathophysiological disruption of the glucose and ascorbate homeostasis [1]. Dengue and Lassa viruses also incorporate phosphatidylserine in their envelope and bind to TIM-1 and Axl receptors for entry, although the main routes for entry are different [1]. The exonuclease domain of LASV nucleoprotein (ExoN) is the primary IFN antagonist, acting as a 3'-5' exonuclease that digests double stranded RNA, effectively hiding the virus from host sensors like RIG-I. LASV Z-protein further suppresses the immune response by directly interacting with the CARD domains of RIG-I and MDA5, blocking their signalling pathways [60,61]. The activity of the exonuclease is also critical for viral replication. Ascorbate and hyperglycaemia have in this case the same described effect on IFN signalling. Again, ascorbate could have a therapeutic impact, since the ExoN activity is dependent on divalent metal ions for catalytic function, with a two metal-ion mechanism utilizing manganese (Mn^{2+}) or Magnesium (Mg^{2+}) while zinc (Zn^{2+}) binding site stabilizes the structure of the domain. Zn^{2+} -binding sites usually involve Cysteine residues, which are highly sensitive to redox state changes, as already mentioned. The viral budding of Lassa virus is dependent on the activity of ExoN protein, that requires divalent cations [62–64]. The mobilisation of divalent cations from the endosomal compartment into the cytosol is mediated by the ZIP (influx into cytosol) and ZNT (efflux from cytosol) families of transporters. A unique feature of ZIP14 SLC39A14 is its upregulation by proinflammatory conditions, particularly increased interleukin (IL-6) and nitric oxide. According to Tolunay Aydemir and Robert J. Cousins [65], ZIP14 expression was IL-6 dependent, and mice treated with IL-1 β showed increased ZIP14 expression and zinc uptake. The effect of ascorbate on redox state, decreasing oxidative stress, ROS species and inflammation, could counteract the virus blockade of IFN signalling, by limiting the availability of divalent cations (Zn^{2+} among them) for the nucleoprotein of Lassa virus.

3. Concluding Remarks

Assuming the implications of this hypothesis, supportive care of EBOV haemorrhagic fever could be significantly improved, acting on the metabolic keys that govern the pathophysiological process. A treatment strategy would focus on the administration of glucose or insulin at convenience, in order to maintain constant and normal levels of glucose in plasma, and on the administration of sufficient quantities of ascorbate and glutathione (which participates intracellularly, along with NADH, in the reduction of DHA to ascorbate) in order to combat the oxidative and inflammatory stress, and avoiding its worst consequence: septic shock. Maintaining ascorbate levels could mitigate the “scurvy-like” vascular collapse during infection. It would have influence on the immune response, improving the lymphocyte status and counteracting the cytokine storming, and would even contribute to an increase in the adaptive immunity and IFN-mediated antiviral action. As it has been showed, ascorbate could interfere with viral budding and oppose viral dissemination.

Future Perspectives

There is a need to confront experimentally the hypothesis of the viral GP interaction with Glut-1 for Ebola virus and other haemorrhagic fever causing viruses, and to confirm many of the predictions and assumptions made by this analysis. Clinical data about ascorbate administration to patients and maintaining normal and constant levels of glucose in plasma, in relation to disease outcome and progression, would be of great interest. The picture could be completed with the study of the described molecular mechanisms of pathophysiology.

As the study of virus-host interactions progress in the future, it would be some day possible to make a classification of viruses according to the metabolic key factor they disrupt or interplay with.

There are no conflicts of interest related to this work.

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