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Chapter 6

Roles of VP35, VP40 and VP24 Proteins of Ebola Virus in Pathogenic and Replication Mechanisms

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Abstract

Ebola epidemic is a fatal disease due to Ebola virus belonging to Filoviridae; currently the viral evolution caused more than 50% of death worldwide. Among the eight proteins of ZEBOV, there are four structural proteins VP35, VP40, VP24, and NP, which have important functions in the intercellular pathogenic mechanisms. The multi-functionality of Ebola's viral proteins allows the virus to reduce its protein number to ensure its proper functioning and keeping the compact structure of the virus. Therefore, the aim of this chapter is to study the mechanism of replication and the roles of VP30, VP35, NP, and L in this process. We provide as well to highlight the influence of the virus on the immune system and on the VP24.

Keywords: Ebola, VP35, VP40, VP24, pathogenic, replication, mechanisms, immune system

1. Introduction

Ebola is an acute viral disease that has appeared in 1976 in two simultaneous outbreaks, Nzara, South Sudan, and the other in Yambuku, Democratic Republic of Congo. The latter occurred in a village near the Ebola River, from which the disease takes its name "Ebola virus" which is an endemic virus of Africa. However, Ebola virus is a member of the filovirus family, characterized by multifunctional proteins. From the appointment of this family, these viruses are filamentous, and they present various forms such as (U), (L) and (6) under electronic micro-

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scope (**Figure 1**) [1]. Thus, viral propagation was due to the variant trips of populations through countries.

Although the multi-functionality of these proteins, each type has a specific role such as, GP protein that ensure important functions in the extracellular environment; otherwise, the VP35, VP40, and VP24 proteins have intracellular roles. eVP35 is usually used as symbol for "EBOLA's VP35 protein," one of the most important structural proteins of ZEBOV having diverse functions in pathogenesis mechanism and viral cycle [2]; it is an indispensable co-factor of replication transcription and an essential member of the replication complex. The virus has two other proteins, which play roles in immune response in intracellular stage.

Thus, the VP24 is a structural protein, that has the ability to internalize the cell nucleus, and known as a minor matrix protein and membrane-associated protein. Then, the latest protein "VP40" is known as a viral matrix protein, and it is the most abundant protein in Ebola's viral structure.

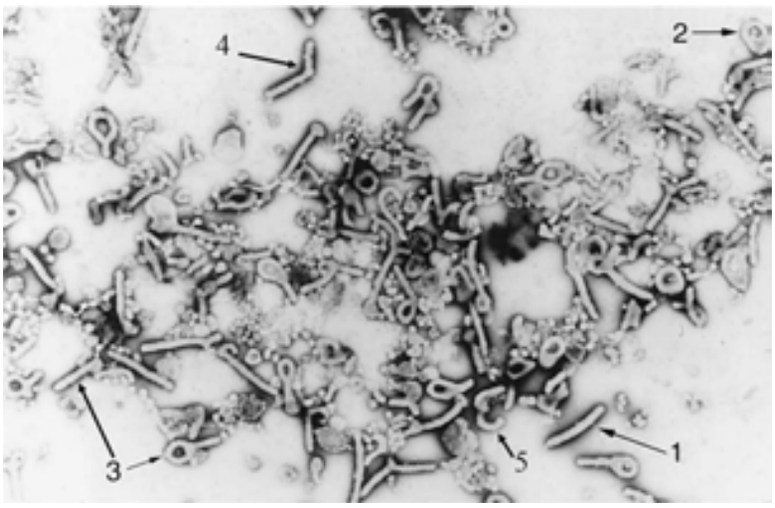

Figure 1. Marburg virus particles purified from the blood of infected guinea pigs, stained by negative contrast medium. Different forms of the virion are shown: 1, rod shaped; 2, ring shaped; 3, mace or (6); 4, (L) form, and 5, (U) form. Shaped '10.000' the virus was purified and concentrated by A, B, et al.; photo by E. Kandrushin, Center for Virology and Biotechnology ''Vector," Koltsovo, Russia) [1].

Ebola is a zoonosis disease. The bats are the main natural reservoir of the virus, while also chimpanzee and some other animals could transmit EBOV virus to human. Transmission modes are diverse and not manageable: contact with fluids of infected persons, possibility of aerosol transmission [3, 4] and contact with infected animals [5]; here we must mention that the religious, cultural and traditional practices help the large propagation of virus among African population and that simple actions can limit the propagation of the virus. Epidemiological studies of WHO and CDC have shown that adults are more subjected to infection than children. Furthermore, Ebola virus can infect both men and women [6]. The virus has the ability to replicate in monocyte-derived dendritic cells without engendering an inflammatory response [7].

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The transmission of Ebola virus to the human body is done by blood and spread in most cells, including vital organs, the infections in brain, liver and the heart disrupted the best functioning of these organs and thus occur as a direct result of death [8]. Time of replication *in vitro* is about 12 hours for Ebola virus on E6 cells [9].

2. How is the Filoviridae evolving?

We can find the answer of this question in phylogenic studies. Generally, the RNA viruses are characterized by the accumulation of many mutations during their evolution—these mutations are not predictable. Therefore, the Filoviridae is divided into genders that are distinct based on the numbers of mRNA encoding by GP gene. A study, demonstrate that the viral genome of this family is very similar. New phylogenetic analysis demonstrated that a few mutations in Reston genome can transfer the virus from non-Human pathogen to a Human pathogen, essentially in the VP24 gene: three VP24 SDPs (T131S, M136L, and Q139R) are likely to impair VP24 binding to human karyopherin alpha5 (KPNA5) and therefore inhibition of interferon signaling [10].

The human body mainly and the general superiors mammals consisting by several systems that achieve different functions to respond in the needs of body and assurance their life, among these systems, there are the immune system which has vital roles and performs important functions in the protection of the body and the eliminations of hazard. The immune system consists of several mechanisms and factors to ensure the proper functioning of the system; they can be subdivided into two under-system: innate immune and adaptive immune. The primary defenses against viral infections are the physical and chemical barriers: skin, pH, acidity, secretion, etc. First, the constituents of the innate response ensure the immune responses against viral agents, before request of the specific answer, another response corresponding to an innate response that is mediated by interferon (mainly interferon-γ), which promotes the activation of NK cells and CD 8 lymphocytes that recognize and destroy cells infected by the virus.

The aim of this chapter is to study the proteins VP35 and VP24 overlooking the immune system. In this chapter, we focus on the structures of those proteins, their roles, and their influence on immune responses.

3. Do the structural proteins have a role in the bending process of Filoviridae without breaking?

More than 50% of the virions grown in cells are polyploidy. Most families of viruses have a single copy of the genome by particle. However, polyploidy is relatively rare in the viral world [11]. Among these families is the *Paramyxoviridae* [12]; so the first assumption is that the Filoviridae are of polyploidy. In addition, the second is the flexibility of the nucleocapsid (RNA, VP30, VP35, N, and L) with the intervention of the VP24 protein [13].

4. Structural and genomic information

The genome of the Filoviridae is rather similar, with seven genes that encoding for the seven proteins or eighth for Ebola. The genes contain the respective open reading frame (ORF) flanked by unusually long non-translated sequences, ranging from 57 to 684 nucleotides [14]. The VP24 protein is expressed by the region 9886–11497, and the region 11498–11501 is an intergenic region, which ensures essential roles for the virus: It is immunosuppressive [15] that allows the virus to control the innate immune system [16]; it binds directly with STAT1 causing antagonize interferon [17]. VP40 has various roles; unmodified polypeptide may assemble into different structures for different functions [18]. The rates of conservation of Filoviridae proteins are 33% for VP35, 27% for VP40, 34% for GP, 33% for VP30, and 37% for VP 24. The board 3′ and 5′ regions ensures important functions in replication, transcription of the genome, and its control.VP35 gene advance by a conserved transcription start and stop signals, "CUACUU-CUAAUU" for start and "UAAUUCU" as stop transcription signal. However, the coding start of VP40 is "CUACUUCUAAUU," and then signal stop is "UAAUUCU." For the viral protein 24 (VP24), the signal start "CUACUUCUAAUU" is sited in position 9886–9897 from Genome's Ebola. However, the VP24 has two stop signals "UAAUUCU" [19]. The genome of EBOV is schematically shown in **Figure 2**.

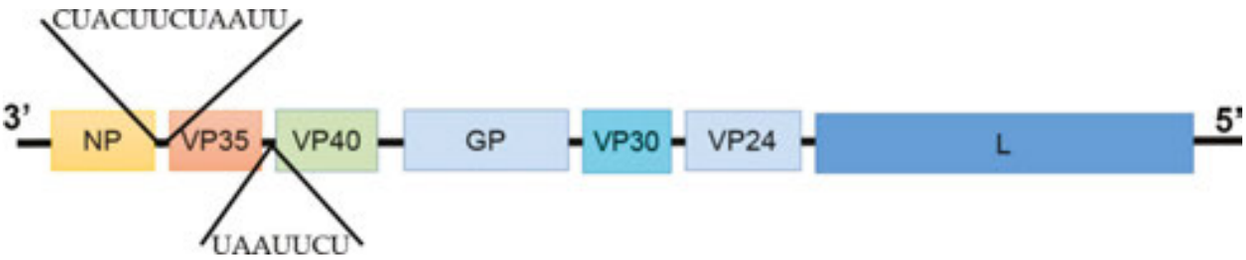

Figure 2. The full-length genome of Ebola is about 19,000 nucleotide, where L gene coding for the RNA polymerase, it is the length gene and more conserved gene in the Filoviridae, then the VP40 is the more polymorphism gene.

The VP35 gene located among the position 3032 and 4407 of Ebola genome, coding for alone mRNA with same length, though the regulatory region is located at the nucleotide 3032 and 3048 "CUACUUCUAAUU" which is a transcription start signal. For the VP40, it is sited at the 4390th nucleotide and 5894th, with one mRNA at the same length, and thus the start signal is on position 4390th to 4401th; besides region 4397–4407and 5883–5894 in genome are two poly-adenine signal sequences [20].

A single mutation in the central basic patch residue R322 or end-cap residue F239 to alanine capable to disrupt the dsRNA binding and alters VP35 inhibitor of RIG1 [21, 22]. These mutants retain modest inhibitory activity relative to the empty vector control. Thus, they exhibited reduced suppression of SeV-induced IFNα/β production [23].

The dsRNA-binding cluster is centered on Arg-312, a highly conserved residue required for IFN inhibition. Importantly, the stability of the β-sheet subdomain structure of VP35 requests an interaction between the side chains of Pro-315, Pro-318, and Lys-339 residues and conserved

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Trp-324, as well as the Ile-340 residue, which make bond with Phe-239, Leu-242, and Ile-278 (**Figure 3**). These residues are highly conserved in Ebola genome, and that demonstrates the importance of these residues in the stability and the good functioning of the VP35 protein [24].

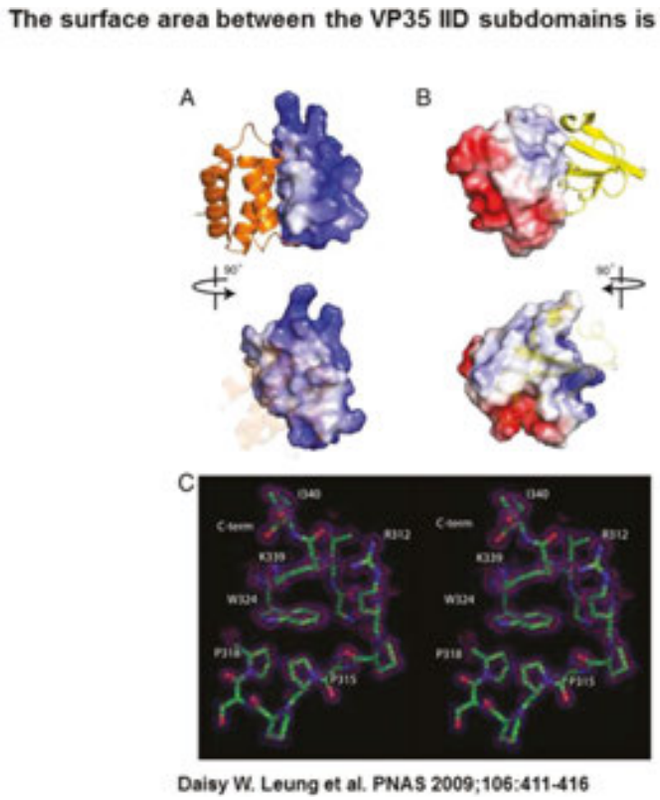

Figure 3. The surface area between the VP35 IID subdomains is hydrophobic. (A and B) Electrostatic representations of the inter-subdomain interaction surface for the α-helical subdomain (A) and the β-sheet subdomain (B) reveal hydrophobic surfaces buried between the two subdomains. Red, white, and blue represent negative, neutral, and positive electrostatic potentials, respectively (range -5 to +5 kT). (C) Stereographic image showing the Trp-324 side chain making important hydrophobic contacts with residues in β4 strand, α5 helix, and PPII [24].

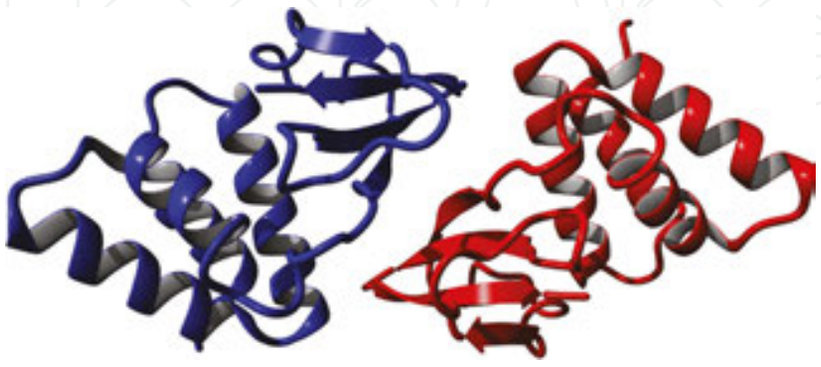

Figure 4. A crystal structure of VP35 from RCSB databank number 4IBB, obtunded X-RAY DIFFRACTION method with a resolution of 1.84 Å R-Value Free: 0.233 and R-Value Work: 0.177. The VP35 has two sub units with 4 β-sheets and 4 α helices [25].

The work of Mateo et al. 2010 [25] has dismiss that the amino acids in position 1–20 of VP24 are not important in the functioning of VP24 to inhibit IFN-β-induced gene expression. However, mutations in position 44 influence on the function of VP24 and have a critical role in the inhibition of IFN-β-induced gene expression. However, residues 142–146 are important to inhibit ISG54 activation by IFN-β. Therefore, mutations at residues 142–146 are able to increase the expression of ISG54 reporter up to 90%, thus drastically reducing VP24 activity [26]. Structure of VP24 dimer is shown as **Figure 5**.

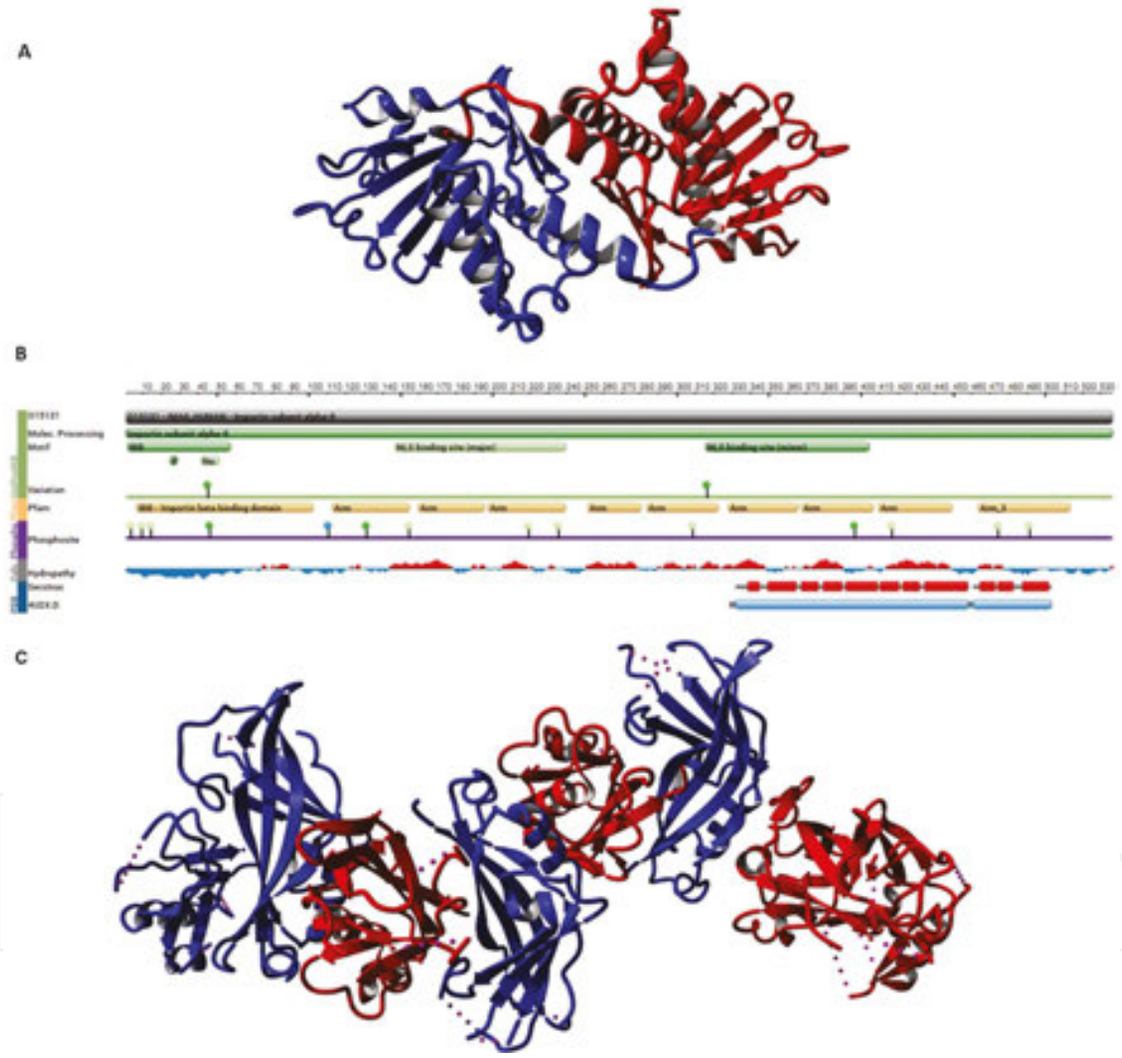

Figure 5. *(A) Ebola virus VP24 structure (4M0Q) from RCSB with (B) resolution of 1.92* Å*, then b. is Protein Feature View—UniProtKB AC: Q05322. The VP35 has two subunits with 8 β-sheet and 5 α helices. The length amino acids chain is 251AA [27]. (C) Crystal image of VP40 Hexamer [29].*

Residues 213–326 are essential for VP40 to associate with liposomes; 309–317 has a critical role in the associated with the DSM fraction; the truncation of 18 C-terminal residues resulted in predominantly oligomeric protein that mainly associated with the DSM fraction [28].

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5. Ebola virus replication

The replication process in the mono-nonsense-negative genome is almost similar; the first step is the transfer from negative sense genome to positive sense genome. The positive sense genome (call also anti-genome or complementary genome) is the complement RNA sequence, direct sense of transcription. From the positive sense genome, two processes are done: the first is replication and getting the negative sense genome for formation of new virion, the second calling the cellular ribosome for the translate process for making new viral proteins (**Figure 6**).

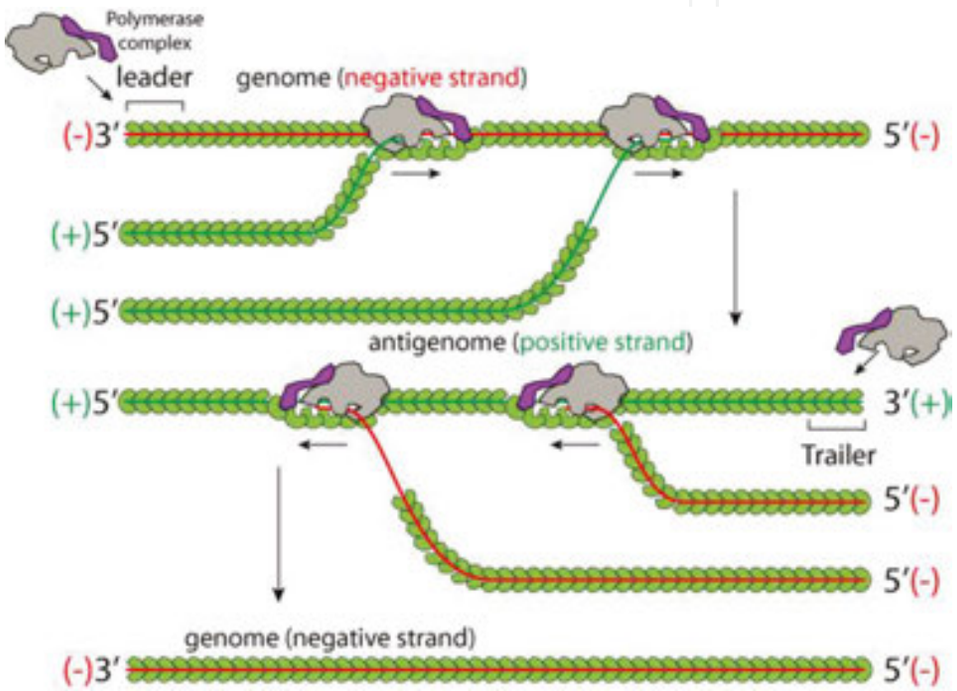

Figure 6. The transcription and replication process, the virus pass from negative sense to positive and from positive to negative sense [30].

The Ebola virus life cycle can be spread over following stages: the first stages are adsorption and penetration in the cell, followed by de-capsulation, transfer genome from negative to positive, primary and syntheses transcription of functional proteins, second transcription replication and assembly of virus.

For Ebola virus, after the liberation of VP30, VP35, L, VP40, and VP24 with the genome in cytoplasm, the first step is the formation of replication complex composed by L (RNA polymerase), VP35, NP, and VP30. The VP30 is an indispensable co-factor of transcription, even the VP30 is part of this complex as transcription activator, and it is a highly phosphorylated [31]. The L is the polymerase protein of EBOV; it is the large protein in genome and the most conserved protein among Filoviridae. In addition to the transcription and replication functions, it can connect the VP35 and NP where NP-RNA helices associate with VP35. Ebola virus VP35 is essential for nucleocapsid formation, together with NP and VP24 [32].

The initiation of transcription requires a VP30 signal, and this signal takes place after attachment of zinc molecule in zinc-binding Cys3-His motif comprising amino acids 68–95 [33]. The phosphorylation site is a conserved site, where a simple mutation can get negative effects on the incorporation of VP30 with the other viral particles and therefore affect the efficiency of the recovery of the viruses [31]. The frequency of transcription of an mRNA is different following the position of the gene in genome, the genes proximal to 3′ are more translated than those in 5′, thanks to the second mRNA produce and that contains essentially [34]. The interagency regions ensure a role in the control and the regulation of replication and transcription of virus [35].

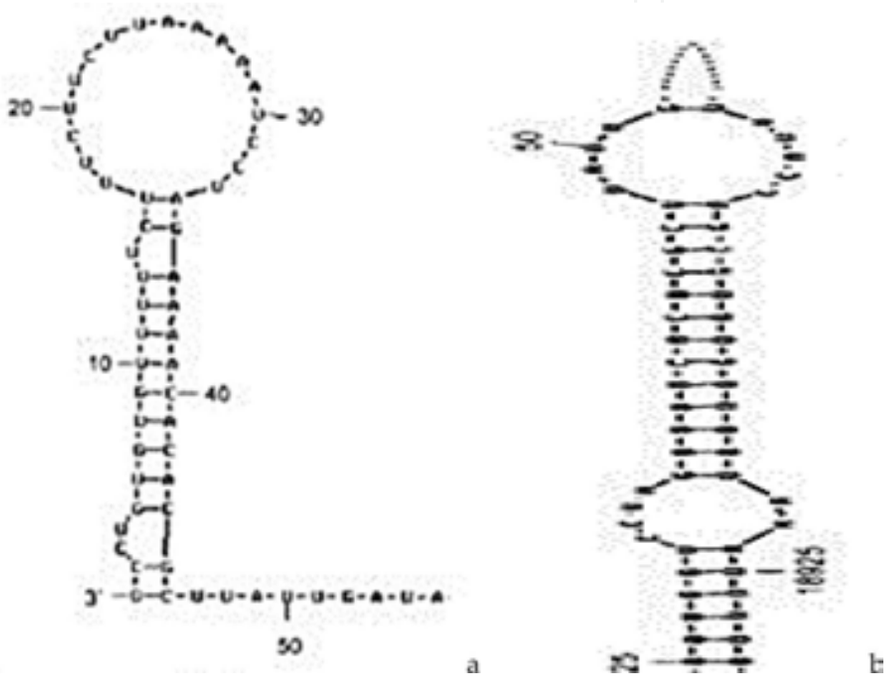

Figure 7. Two secondary structures predicted of ZEBOV genomic RNA. The interactions made by (a) a hairpin structure (b) and panhandle structure format [33].

The RNA bonds with the complex of VP35-NP-L to initiate the replication and transcription of viral genome. Translation of viral protein is ensured by liberation ribosome in cytoplasm. The replication mechanism is not manageable enough; however, there are estimates of the true mechanism of replication.

Weik and their collaborators in 2005 [36] demonstrate that the nucleotides 5–44 of the EBOV leader are involved in RNA secondary-structure formation; the alteration of 36 nucleotides spanning the region 55–90 did not affect replication. However, when the random sequence was elongated by four additional nucleotides, replication activity could not be detected. Bipartite promoters localized in 3′ of gene, and then the second signal is in the beginning of the next gene; it is a succession of eight UN5 hexamer repeats (**Figure 7**) [36], other research shows that EBOV NP is inactive in Marburg the vice-versa, and this suggests that they present a specific motifs by the complex of replication for each gender. The region of the EBOV

promoter start signal of the NP gene (12 nucleotides) and the following 13 nucleotides has been shown to form a stem-loop structure, which is involved in regulation of VP30-dependent transcription [1]. Other results of Brauburger et al. 2014 [37] reflect fundamental differences in the control of polymerase behavior by cis-acting sequences between viruses with conserved and variable gene borders and suggest an important role of conserved IRs in transcription regulation, while the function of variable IRs remains less clear.

6. Ebola and immune system

The Ebola virus has the ability to flare the immune system by several modes. Furthermore, the virus uses the immune system as tools to fix and internalize in cell, thanks to the link between GP and the antibody as demonstrated in the chapter of Glycoprotein. Mahanty and others [38] illustrate in the **Figure 8** some immune evasion tools [38].

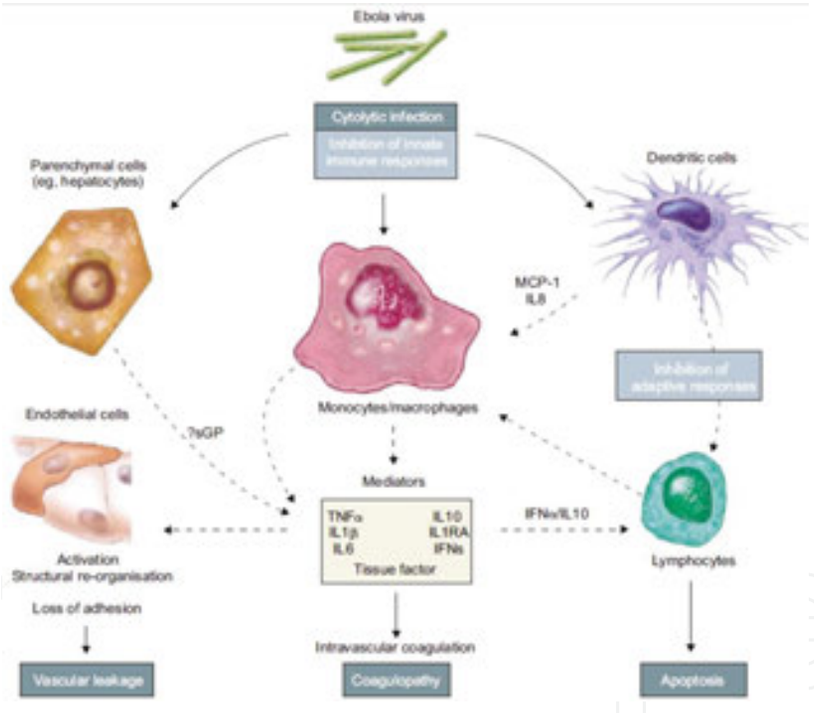

Figure 8. A model of the pathogenesis of filoviral hemorrhagic fever, based on studies of Zaire Ebola virus infection. Infection causes lysis of monocytes/macrophages, dendritic cells, and hepatocytes and suppresses innate immune responses in these cells, aiding further dissemination. Direct injury to infected cells is accompanied by indirect effects that are mediated by pro-inflammatory and anti-inflammatory effector molecules, including interleukin 1 (IL1), interleukin 6 (IL6), TNF, interleukin 10 (IL10), and type I interferons (IFN). The severe illness results from the combined effects of widespread viral cytolysis and massive release of pro-inflammatory mediators. Pro-inflammatory cytokines and chemokines are also produced by activated endothelial cells, resulting in a feedback loop to the monocytes/macrophages. Lymphocyte apoptosis is also apparently brought about through effects of pro-inflammatory mediators; it may contribute to immunosuppression by weakening adaptive immune responses. The cell-surface expression of tissue factor by virus-infected monocytes/macrophages induces disseminated intravascular coagulation. MCP monocyte chemoattractant protein; IL1RA interleukin-1 receptor antagonist [39].

Here, we discuss the intracellular mechanism to escape the immune system via structural proteins and their roles in inhibition of the interferon's expression (**Figure 9**).

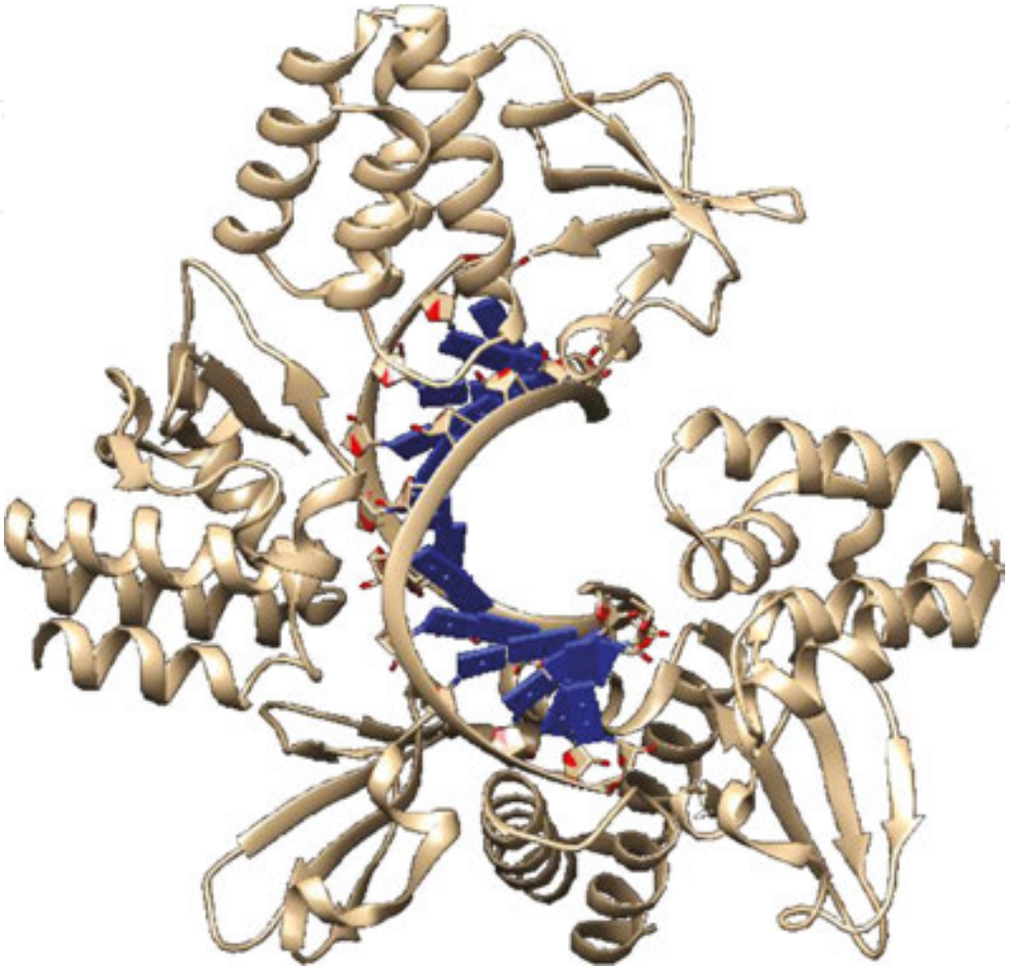

Figure 9. The crystal structure of VP35 bond to dsRNA [41].

The VP35 implicated in modulation of the host immune response. Studies show that the region C-terminal-binding site with the dsRNA in VP 35 is being demonstrated as responsible of antagonism region's interferon and immune evasion. The VP35 bond specifically with specifically with poly(rI) poly(rC), poly(rA), poly(rU) [39].

The VP35 through PACT has the ability to inhibit the retinoic acid inducible Gene-I (RIG-I) to bind with the dsRNA, and this action inhibits the transfer of hazardous signal to the interferon promoter simulator I by RIG-I in first time. Therefore, if the signal has transferred by the RIG-I, the VP35 binds to the Tank-binding kinase-1 interferon kinases (TBK-1/IKKε) and inhibiting the phosphorylation of IRF-3/7 [40–43]. Consequently, the translocation nucleus of signal and the expression of INF-β will be inhibited (**Figure 10**). More recent study suggests that other filoviral proteins, including EBOV VP30 and VP40, also counter the RNAi pathway [44].

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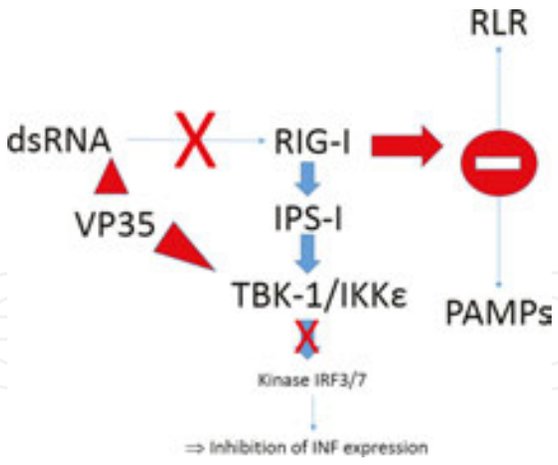

Figure 10. The inhibition of the recognition of PAMPs by the RLR, due to the inhibition of RIG-1 by bonding of VP35 to dsRNA through the CBP.

However, Luther and their collaborator's in 2013 [45] had shown that the PACT also implicated in inhibition of RIG-I. Other studies shown that the mVP35 and eVP35 effects differently the RIG-I, ebolaVP35 blocked the RIG-I then Marburg VP35 decreased the affinity and the activity of RIG-I [46].

The same context of INF-β's inhibition, the VP40 interacted with the Janus kinase/tyrosine kinase II (JAK I/TRK II) for block their phosphorylation and as results, inhibition of the activation of STAT heterodimer kinase require the phosphorylation of JAK-I/TRK II [47, 48].

In the other hand, VP24 bonds with Karyopherin-α by the residues in activation of sites 26–50 and 142–146 and they are demonstrated to be the most important residues for this activity (**Figure 11**) [46].

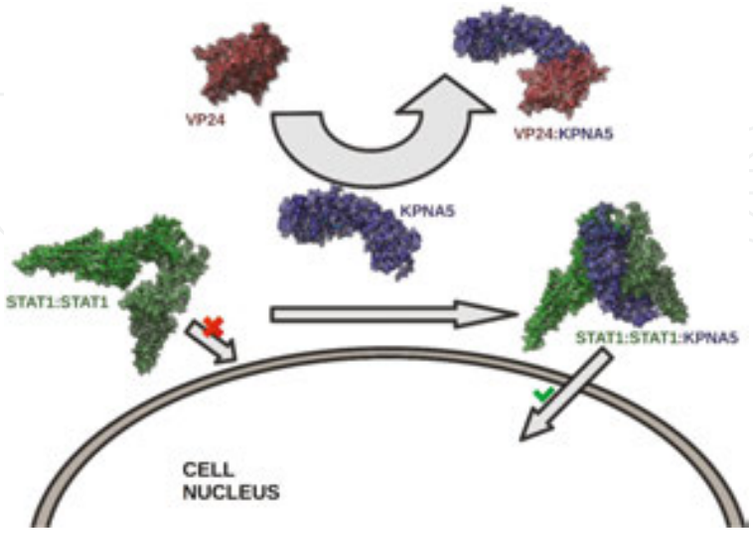

Figure 11. The binding between VP24 and KPNA5, *and* this link in the active site of STAT homodimer. It prevents the adhesion of the SATA homodimer phosphorylated and thus lack the protein's ability to enter the cell nucleus.

7. Inhibition strategies of Ebola virus

The involvement of VP35 in diverse parts of the infection (replication, inhibition of RIG1, TAK, and inhibition of interferon) made it a principal target of several medicines to inhibit it. Thus, all the Ebola proteins are crystallized and available in databases as RCSB, addition to the full-length genome sequenced is available in NCBI databases make research and information about the virus more accessible (**Figure 12**).

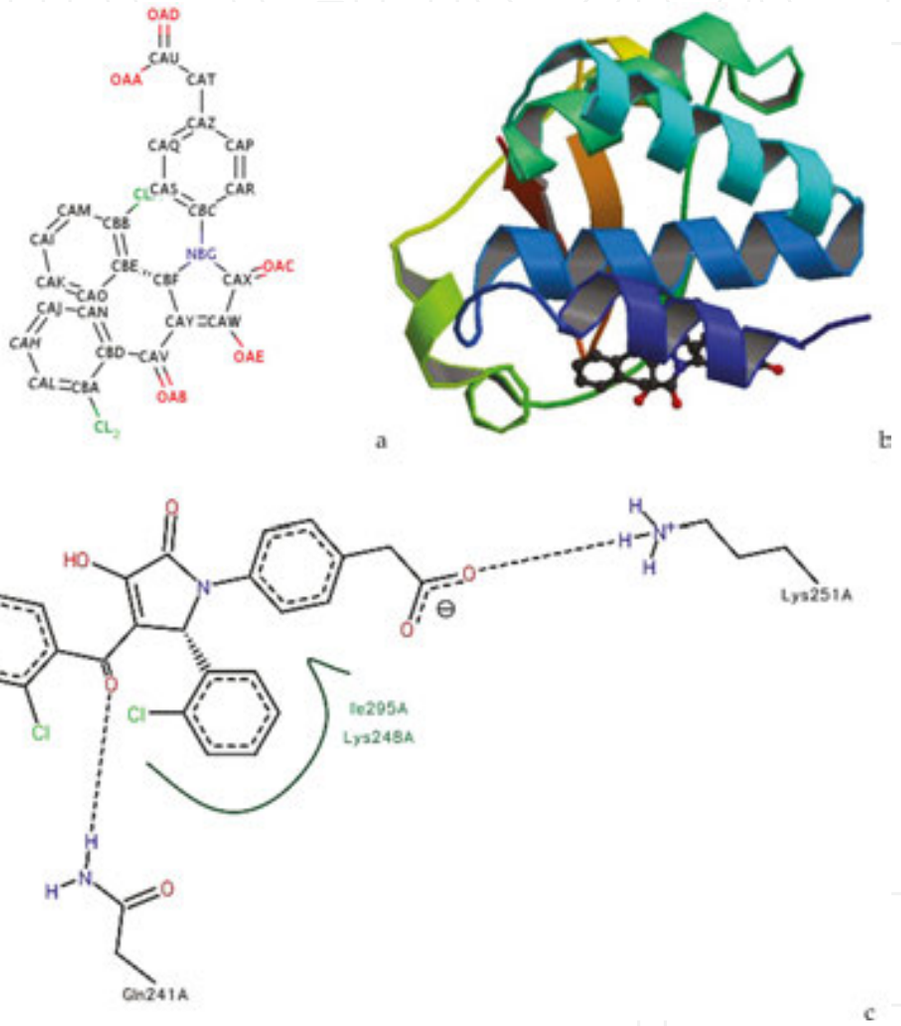

Figure 12. In silico-derived small molecules, it binds the filovirus *VP35* protein and inhibit its polymerase cofactor activity. (a) {4-[(2R)-3-(2-chlorobenzoyl)-2-(2-chlorophenyl)-4-hydroxy-5-oxo-2,5-dihydro-1H-pyrrol-1-yl]phenyl}acetic acid. (b) *3D with ligand.* (c) The *pharmacophore map of ligand in the active site of VP35* [49].

8. Conclusions

The light of the above discussion results, the Filoviridae genome coding seven proteins, with the exception of Ebola virus that coded for the eight proteins, including the GP gene which

coded for secretory glycoproteins, membrane glycoproteins, and thus it is subdivided into subunits called as GP1 and GP2. However, the sGP has not the membrane region. The Ebola genome contains six interagency regions, having functions in regulation of transcription of genes and the CAP-polyA to protect the mRNA. Those regions contain a RNA 2D confirmation boots. The immune evasion processes in Filoviridae generally, and essentially for Ebola virus based on two complementary process; one intercellular by GP and second intracellular where the roles remarkable of VP35 by inhibition of RIG-I and INF-3, therefore, the roles of VP40 and VP24 inhibition of INF-β signal.

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