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The Effect of Ebola Virus on Human Immune System

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Abstract: Ebola virus disease, formerly known as Ebola hemorrhagic fever, is a rare but severe disease which is often fatal in humans if untreated. Ebola was first identified as a possible new "strain" of the Marburg virus in 1976 which caused two simultaneous outbreaks, one in Nzara (South Sudan) and the other in Yambuku (DRC). The International Committee on Taxonomy of Viruses (ICTV) identified Ebola virus as species, Zaire Ebola Virus which belongs to the family Filoviridae. Ebola virus contains a Negative-sense, single stranded RNA and it encodes for seven different proteins including one extrinsic protein, glycoprotein and six different intrinsic proteins, VP24, VP35, VP24, VP40, VP30, Nucleoproteins, L-polymerase. EBOV infection obstructs DC maturation without inducing cytokine expression, leading to impaired T-cell proliferation. Whereas macrophages produce selective proinflammatory cytokines and certain tissue factor which attract additional target cells that in turn induces vasodilation and causes vascular permeability and disseminated intravascular coagulation. There are a few treatment methods which have been proven effective against the Zaire EBOV and some monoclonal antibody-based drugs have also been used. Only one FDA approved vaccine, rVSV ZBOV is available.

Keywords: Ebola virus, Filovirus Hemorrhagic fever, intrinsic proteins, monoclonal antibodies.

I. INTRODUCTION

Ebola Virus Disease is a viral hemorrhagic fever which is zoonotic in nature. Bats are considered as the natural reservoir for the Ebola virus. Since Ebola virus belongs to the family of Filoviruses, the genetic material consists of single stranded RNA in negative sense surrounded by nucleoproteins and along with several other proteins as discussed below in its vicinity. Mode of transmission is by means of body fluids, say, blood of the infected individual. Ebola virus enters the patient through mucous membranes, breaks in the skin, or parenterally (semen, breast milk) [1].

The cells affected include dendritic cells, macrophages, endothelial cells. Lymphocytes aren't affected by EBOV, but due to the lack of release of costimulatory molecules, these cells die. Thus, lymphocytopenia is observed in most of the cases. Ebola virus migrates from the initial site of infection to the closest lymph node and finally it reaches the liver. Here, it carries out its replication at the cost of necrosis of hepatocytes. This is associated with clotting factors not functioning properly and this subsequently leads to coagulopathy.

Studies show that the cells affected majorly by the Ebola virus are dendritic cells and macrophages. Infection of macrophages leads to selected suppression of proinflammatory cytokines. Dendritic cells on the other hand release a limited range of chemokines, fail to release costimulatory molecules required to activate T-cells. Macrophages then initiate disseminated intravascular coagulation (DIC). The response of dendritic cells is crucial for estimation of the outcome of this infection [2].

II. SURFACE AND INTRINSIC PROTEINS OF EBOLA

Ebola virus consist of a single stranded RNA genome. The genome of EBOLA consists of 7 main proteins which are NP (nuclear proteins), Viral Proteins- VP35, VP40, VP30, VP24, GP (Glycoproteins) and L polymerases. Each protein has got its specific function. These proteins play major role in evading the immune system [3].

VP24, VP35, VP40 and NP are the four structural proteins of ZEBOV which play a major role in intracellular pathogenic mechanism. These proteins are present in less number in the Ebola virus due to the multifunctionality of proteins which allows the virus to maintain lesser number of proteins for proper functioning and maintaining the tight structure of virus. The VP24 and VP40 are the proteins which have roles in intracellular stage in immune response, whereas VP35 is the most precious structural protein of ZEBOV, which have large number of functions [4].

At present, the recent researches have studied a great number of new roles of these proteins. Each function of EBOLA is being worked upon by more than one protein suggesting co-working between these proteins.

We examine the collection of recently identified secondary functions of ebolavirus proteins in order to provide better understanding of roles of each protein in viral replication and pathogenicity. Each function of EBOLA is being worked upon by more than one protein.

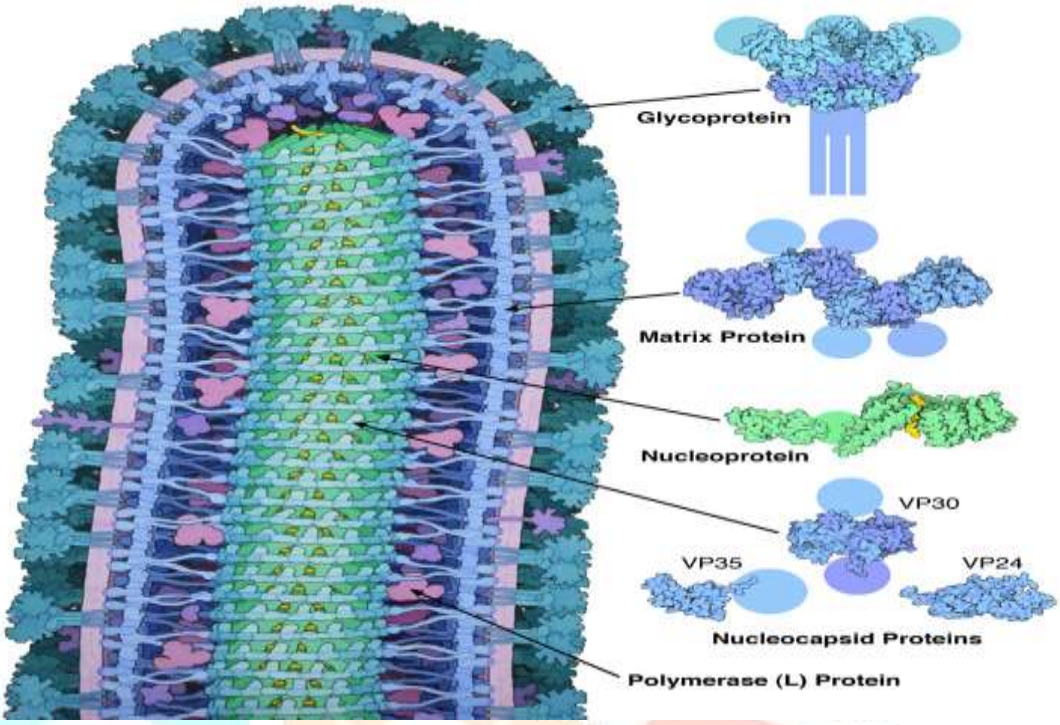

Figure1-The diagrammatical representations of the viral proteins on Ebola virus. [5]

Let's start from the entry of virus into the host cells which is mediated by glycoprotein.

a. Glycoprotein (GP)

GP plays an essential role in attachment to the viral surface. EBOV mainly enters cells via GP-dependent micropinocytosis. but based on the form of host cells, there are other ways to enter too [6]. There are three different types of GPs consisting of GP1, GP2, sGP (soluble) and ssGP (small soluble GP) [3-4] [6-7]. After entering the cell, the viral genome needs to get out of the lysosome it's trapped in. So, GP mediates fusion NPC1 and viral membrane in order to release the genome. It is capable of creating pores in the plasma membrane of mammalian cells, raising the permeability of ions and inducing cytotoxicity. The expression with VP40 is enough to generate VLPs, but expression with GP improves VLP production, suggesting a secondary function. Findings show that TNF-α-converting enzyme (TACE) cleaved GP on the cell plasma membrane, leads to the release of a soluble cleaved compound named shed GP. It is thought to activate macrophages by binding and triggering toll-like receptor 4 (TLR4) in a manner which needs GP glycosylation [6].

b. Viral Protein 35 (VP35)

VP35 is the most important protein of the EBOLA Virus. It plays a major role in due to its diverse functions which includes

Blocking interferon induction, by binding to double stranded RNA and the development of IFN-α/β gene is induced by Retinoic acid inducible Gene-I(RIG-1). The VP35 directly binds to PKR 1 activator (PACT) preventing it from binding and activating to RIG-1, by this way VP35 inhibits RIG-1 activation which indirectly blocks IFN induction. [3-4] [6-9]. It acts as a polymerase factor in RNA polymerase transcription and replication complexes [3-4] [6-9]. The dendritic cell maturation is inhibited by VP35.The VP35 protein stop the virus –stimulated expression of costimulatory molecules (CD40, CD86, CD80), MHC-class II, Cytokines (IL-6, IL-2) and (TNF- α), including IFN-α/β in an immature dendritic cell [7].

c. Viral Protein 24 (VP24)

This protein is also known as minor matrix protein and membrane associated protein [3].

The two major functions of VP24 is to block interferon signaling and virion assembly. The VP24 evades the host cells (Dendritic cells and macrophages) and inhibits gene expression of IFN TYPE 1 and 3 protein. This will indirectly block the STAT1 Gene (which is necessary for) and its nuclear import [3-4] [6-7] [9].

Recent data suggest that VP24 is also capable of blocking IFN induction by suppressing NF-kB (a transcription factor) activation following stimulation of the TNF-α and suppressing the retinoic acid-inducible gene I (RIG-I)–dependent activation of gene expression IFN- γ1 [6]. Therefore blocking/suppressing/inhibiting all the different proteins ZEBOV takes over the entire immune system. As said earlier, Each ZEBOV protein has more than one function. The secondary role of VP24 is virion assembly.

VP24 has an important role in virion capsid assembly. The major component of nucleocapsid assembly are known as NP and VP35, although VP24 is weakly associated but it acts as catalyst for particle formation [6][3].

d. Viral Protein 40 (VP40)

The VP40 is known as viral matrix protein [3]. VP40 protein takes part in budding and virion assembly [3-4] [6]. IFN in the form of a hexamer VP40 takes part in virion assembly and if in an octamer form, it takes part in genome replication and RNA binding [6]. Entry of VP40 exosomes in the naïve T lymphocytes and monocytes lead to apoptosis and reduced cell viability [6]. VP40 is not the only protein to take part in viral replication and transcription process. The major proteins involved are VP30 AND L PROTEIN [3-4] [6].

e. Viral Protein 30 (VP30)

VP30 is a minor nucleoprotein [3]. VP30 is also known as transcription activator which simply means that it starts the EBOV transcription process [3] [6-7]. VP30 is a phosphorylated protein, whereby phosphorylation has a negative impact on transcription, thus allowing binding to NP [6]. VP30 also facilitates RNA binding and increases viral genome transcription and it takes part in silencing of cellular RNA [6]. The L protein forms an RNA dependent RNA complex (RdRp) with VP30 to perform transcription and replication of the viral genome [4] [6].

f. Nucleoproteins (NP)

As said earlier, Nucleoprotein (NP) is one of the major structural protein in nucleocapsid in virion assembly [3] [6]. This protein fastens the viral replication and transcription of ZEBOV genome as it is the main component of viral ribonucleoprotein complex and it plays major role in mediating genome encapsulation during virus assembly and in defending vRNA from degradation [3] [6-7]. Along with NP and VP35, VP40 also takes part in virion assembly [3].

g. L polymerase

L-polymerase is a part of RNA dependent RNA COMPLEX (RdRp) and is important for replication and transcription process of viral genome [3-4] [6]. L also takes part in transcription editing and it edits mRNA. Due to L transcriptional editing, the GP gene has been shown to encode for three different products: full length GP, consisting of GP1 (receptor binding) and GP2 (viral fusion) subunits; soluble GP (sGP), lacking the transmembrane domain; and small soluble GP (ssGP) [6]. Each and every virus possesses its genetic material along with other intrinsic proteins and factors that help it in its replication once its inside the host cell.

Recent findings about Ebola virus suggest these proteins can not only help in replication, but also have been successful in modulating the host's immune responses in their favor in many ways. In the following sections, it is discussed that how these proteins go on to have an impact on the cells majorly affected by this virus, macrophages and dendritic cells.

III. EFFECT OF EBOLA VIRUS ON DENDRITIC CELLS

The stimulation of antigen specific immunity is taken care by the DCs as they are considered "The brains" of the immune system. The outcome of the ZEBOV infection is based on them as their response is crucial [10]. Ebola virus replicates capably inside the dendritic cell without altering other cells in the immune system, specifically the T cells [11]. It obstructs DC maturation without inducing cytokine expression, leading to impaired T-cell proliferation [2].

Recent studies have exhibited that lipid rafts are used for the entry and egress of filoviruses from cells. Physiological functions like cell-to-cell communication and signal transduction is one of the important biological functions of these cholesterol-enriched microdomains [11]. Because of the assembly and release of the filovirus virions is through the lipid-raft microdomains, it may permanently disorganize the morphology and composition of the rafts, resulting in the suboptimal signal transduction and cell-to-cell communication. This offers an explanation so as to why the impairment of the ability of DCs is seen to process and present antigens [11].

At the point when presented to the infection, there is a rapid uncontrolled secretion of proinflammatory cytokines and costimulatory particles because ZEBOV infection partly impairs both the cells i.e. DCs and macrophage, and cannot prevent the systemic spread of the virus therefore they initiate inflammation and coagulation. Still, suppression of the adaptive immunity is seen later, despite of the continuous release of inflammatory mediators which is evidenced by the low specific Ab [12]. These seemingly contradictory cellular and molecular mechanisms that underlie these immune states are unknown [2].

There are different proteins present on the viral surface as discussed above. VP35 is the viral protein that impairs the maturation of DC. This viral protein inhibits the expression of CD40, CD80, CD86 and the MHC class 2 (major histocompatibility complex), when expressed in immature DCs [13]. Also, there is a small increase seen in CD86 and HLA-DR, no increase in CD83 and no downregulation of CCR5 on the surface of DCs [11]. Cytokines such as interleukin IL-6, IL-12, TNF (tumor necrosis factor) alpha and alpha/beta interferon (IFN-alpha/beta) are also suppressed. Moreover, the capability of the DCs to initiate the activation of the CD4+ T cells is also diminished.

The inhibitory effects of VP35 is only partly reversed during the addition of type 1 IFN to immature DCs [13]. Additionally, the functions stimulated by lipopolysaccharide, a protagonist of toll-like receptor 4, is also disturbed. A major contribution to the profound virulence of Ebola virus infection may have VP35 in viral interference in DC function with resultant deficiency in T-cell function in a critical role [13].

Despite the lack of infection of T lymphocytes, infections with EBOV ultimately leads to "immune paralysis" which is characterized by deficiency in T lymphocyte responses, T lymphocyte apoptosis and lymphopenia [12]. Whereas, dendritic cells along with the macrophages

are the initial targets of the virus and therefore do not undergo a typical maturation process [3]. Notably, deactivated preparations of EBOV, inhibits activation of DC in response to other stimuli and also fails to stimulate human DC. Either T lymphocyte survival or apoptosis is promoted by DC, this depends on their maturation state and the presentation of antigen [12]. Lymphocyte apoptosis starts early in the infection like coagulation abnormalities.

Mediators like TNF- alpha, Fas and its ligand, TNF alpha related apoptosis ligand (TRIAL) are secreted by the virus infected macrophages and may be capable of inducing apoptosis [10]. Apoptosis can be overcome by a cytokine storm if related to interleukin 2 (IL-2) deprivation. [12] Hence, EBOV may be directly correlated to the lack of proper DC maturation occurring due to a lack of functional T lymphocyte response [12]. The elimination of lymphocytes may also be related to the impairment of the DCs. Lymphopenia is also seen in different viral hemorrhagic fevers, and a large apoptotic lack of lymphocytes large in septic shock, suggesting that similar host responses occur in these conditions [10]. Study of the effect of ZEBOV infection on plasmacytoid DC is needed, because it plays in important part in controlling the viral infections by secreting huge amounts of IFN type 1.

IV. EFFECT OF EBOLA VIRUS ON MACROPHAGES

Infected macrophages cause a noisy production of proinflammatory cytokines, generation and release of vasoactive peptides disrupting vascular permeability, and recruitment of more cells susceptible to EBOV to the site of infection. This creates a positive feedback loop to ensure further viral replication and dissemination. During Ebola virus (EBOV) infection, secreted glycoprotein (sGP) is found in large quantities in the serum of both patients and infected animal models. It is thought to serve as a decoy for anti-EBOV antibodies.

Macrophage polarization and phagocytic capacity of activated macrophages were found to be unaltered by sGP treatment. Although some findings do suggest that polarization into certain phenotypes can lead to viral dissemination. However, treatment with sGP inhibited macrophage production of the pro-inflammatory cytokines TNFα and IL-6 while the yield of anti-inflammatory cytokine, IL-10, remained intact. Interestingly, the migratory ability of macrophages was also diminished by sGP, potentially due to a decrease in expression of CD11b, a vital macrophage integrin. The GP interaction with Toll-like receptor 4 (TLR4) leads to cytokine induction. The proinflammatory communication so begun by the sGP can be inhibited by blocking TLR4 signalling [14].

The human monocytic cell line, THP-1, which can be differentiated into macrophages, which was used as a source of cells. The cells were treated with sGP with either a low or high dose. Production of IL-6(a pro-inflammatory cytokine) by monocytes was not significantly affected by any dosage of sGP. However, the production of IL-6 by macrophages was markedly inhibited in the presence of sGP. Thus, macrophages ended up being affected on any dosage of sGP. These results show that sGP may have a direct role in inhibitory effect on non-infected macrophages.

Macrophage pro-inflammatory cytokine production is inhibited by EBOV sGP if given after activation, but not during activation. THP-1 macrophages when cultured with IFN-γ and later treated with LPS and sGP respectively, showed that sGP inhibited the production of pro-inflammatory cytokines, IL-6 and TNF-α significantly. But it did not affect the anti-inflammatory cytokine, IL-10. These results show that sGP does not inhibit the production of anti-inflammatory cytokines but selectively inhibits the production of pro-inflammatory cytokines.

Activated macrophages fail to react towards MCP-1 (Monocyte Chemoattractant Protein) due to impairment caused by sGP. So, with the impairment of inflammation-related events, the survival and dissemination of virus is promoted. Also, EBOV sGP may be downregulating the expression of integrin protein CD11b which in turn impacts the migratory capacity of activated macrophages [15].

Polarization due to IL-4/IL-13 increases the expression of cell surface receptors like C-type lectin receptor DCSIGN, which are essential for EBOV infection on human MDMs, resulting in enhanced Ebola GP-dependent infection. However, systemic spread of the virus and high mortality suggests that despite the quick action of the innate response, EBOV succeeds in exciting the early host response in order to infect "carrier" cells (i.e. macrophages and DCs) for the purpose of spreading the virus from the site of initial infection [16].

Monocytes do not have a significant impact upon viral replication due to their limited cytokine production and phagocytic ability. So, they are likely not a target of EBOV sGP as they are unable to alter IL-6 production by THP-1 monocytes. On the other hand, upon differentiation and activation of monocytes into macrophages, the production of IL-6 was markedly less in THP-1 macrophages. Thus, sGP impacts macrophages only after differentiation from monocytes. Hence, suggesting that the receptor on which sGP binds is expressed only on differentiated macrophages and not monocytes.

Meanwhile, macrophages are not phenotypically homogenous. Their adaptability to the microenvironments (which includes response to cytokines) with respect to their phenotypes is a remarkable phenotype and is called "MACROPHAGE POLARIZATION". M1 macrophages lead upregulation of a number of proinflammatory genes such as CXCL10, IL-12 subunits, IL-1β, TNF, and IL-6 and perform pathogen removal. M2 macrophages produce a number of immunomodulatory compounds and promote inflammation quality and process of wound healing.

The polarization status of macrophages can influence EBOV infection. It is known that filoviruses encode an antagonist for IFN-γ that blocks an effective M1 polarization [17]. Findings suggest that M2-like polarization of macrophages enhances filovirus infection. VLP and virus entry is increased by stimuluses that polarize M2 macrophages, highlighting the fact that polarization by cytokine changes the susceptibility of these cells for EBOV [18].

The endosomal NPC1, a potential receptor over the exposure to IL-4/IL-13 could certainly enhance the virus entry that could contribute to the enhanced entry upon IL-4/IL-13 exposure. But findings suggest that mannose-binding CLRs are essential for this effect and at least one more step is required to trigger the events of membrane fusion [18].

Modulating the host immune response i.e. handling of certain cytokines in the disease can be considered as a potential treatment option for EBOV disease.

V. TREATMENT AND VACCINE

Symptoms of Ebola virus disease (EVD) are treated as they appear. When used early, basic interventions can significantly improve the chances of survival. These include: Providing fluids and electrolytes (body salts) through infusion into the vein (intravenously), Offering oxygen therapy to maintain oxygen status, using medication to support blood pressure, reduce vomiting and diarrhoea and to manage fever and pain, treating other infections, if they occur [19].

a. mAb114

mAb114 is a kind of monoclonal antibody. This monoclonal antibody is interested in targeting the domain of Ebola virus glycoprotein, thus preventing death. mAb114 has several roles that show its use for treatment in an epidemic. Simplified dosage could ease up the cost of manufacturing treatment courses in response to large outbreaks, such as those observed during the 2014–16 outbreak in west Africa. Monoclonal antibodies can be very effective in treating a disease. It takes one to invest time and resources to manufacture them.

b. rVSV ZEBOV Vaccine

There's only one FDA approved vaccine available and that's the rVSV-ZEBOV. Recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV), also known as Ebola Zaire vaccine live and sold under the brand name Ervebo, is a vaccine for adults that prevents Ebola caused by the Zaire ebolavirus [21-25]. When used in ring vaccination, rVSV-EBOV has shown a high level of protection [26- 28]. rVSV-ZEBOV is a recombinant, replication-competent vaccine[29]. It consists of a vesicular stomatitis virus (VSV), which has been genetically engineered to express a glycoprotein from the Zaire ebolavirus so as to provoke a neutralizing immune response to the Ebola virus[22]. Effectiveness: In April 2019, following a large-scale ring-vaccination scheme in the DRC outbreak, the WHO published the preliminary results of its research, in association with the DRC's Institut National pour la Recherche Biomedicale, into the effectiveness of the ring vaccination program, stating that the rVSV-ZEBOV-GP vaccine had been 97.5% effective at stopping Ebola transmission, relative to no vaccination [27-28]. Side effects: Systemic side effects include headache, feverishness, fatigue, joint and muscle pain, nausea, arthritis, rash, and abnormal sweating [26] [30-31] [22]. Injection-site side events include injection-site pain, swelling, and redness [22].

c. GS-5734 (Remdisivir)

The investigational antiviral agent GS-5734, also known as remdesivir, is being developed by Gilead as a treatment for Ebola virus disease. NIAID is studying its ability to clear Ebola virus RNA from the semen of Ebola survivors. Remdesivir is no longer being administered to patients with Ebola virus disease in the DRC after the preliminary results of the PALM trial were announced. However, the antiviral is being considered for combination therapy, which would need to be explored in preclinical studies first [20].

d. ZMapp

ZMapp is an immune based treatment of Ebola Virus disease. It is a cocktail of three different Ebola-binding immunoglobulin G antibodies, which effectively immobilizes Ebola pseudovirus in human airway mucus when treated with ZMapp. The combination of antibodies used in ZMapp turned out to be the best to control the virus which is c13C6 from MB-003 and two chimeric mAbs from ZMAb, c2G4 and c4G7[31]. These antibodies bind to the surface glycoprotein of the virus thereby inhibiting viral replication. The entire drug production took months to complete and the amount of ZMapp needed at the time of the outbreak was severely surmounted by the spread of Ebola Virus Disease. Even once there is enough ZMapp made, its true effectiveness in humans has yet to be determined [32].

VI. RESULTS AND DISCUSSION

In this study we saw that, when Ebola strikes, it robustly attacks the immune system and some of the first cells that it impairs are Dendritic cells and the macrophages. It leads to the inhibition of the DC maturation and thereby inducing cytokine expression which affects the T cell proliferation. It also impairs the ability of the DC to present and process antigens because of the lipid raft (used for cell communication) used for the entry and exit of the virus, causing permanent damage to its morphology and the compositions. VP35 is the viral protein that impairs the maturation of DC and inhibits the expression of co-stimulatory molecules and the MHC class 2 (major histocompatibility complex). This basically leads to "immune paralysis" which is characterized by lymphocytopenia (of T-cells.)

The other cell type which is largely affected by this infection are the macrophages. The macrophages fail to react towards MCP-1 (Monocyte Chemoattractant Protein) due to impairment caused by sGP. So, with the impairment of inflammation-related events, the survival and dissemination of virus is promoted. Also, polarization into M2 phenotype is known to help viral dissemination. Observations were that IL-6 production in monocytes wasn't hampered at all by sGP, but it was seen in the monocyte derived macrophages (MDMs), suggesting that the proteins that bind to sGP are expressed on macrophages and not monocytes. Migratory capacity of macrophages was seen to be affected largely due to down regulation of integrin protein, CD11b.

As of now, symptoms of Ebola virus disease (EVD) are treated as they appear. At the point when utilized early, essential intercessions can fundamentally improve the odds of survival. The monoclonal antibody, mAb114 competes with the Ebola GP so that it can bind to NPC1 and neutralize the infection. ZMapp contains a mixture of neutralizing antibodies or can be called a cocktail of mAbs that confer passive immunity to an individual. Thus, enhancing the normal immune response. It is designed to be administered after exposure to the Ebola virus. They are intended to attack the virus by interfering with its surface and neutralizing it to prevent further damage.
Remdesivir, a broad-spectrum antiviral drug. In Ebola virus, it is known as an analogue to adenosine and thus competes with ATP during RNA replication. Although it's not properly known if it blocks replication. But it definitely delays the elongation of the newly formed RNA chain. The recombinant vaccines used, expresses EBOV glycoprotein to generate hosts response to neutralize Ebola virus.

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