Review Article

Molecular Strategies of Ebola Virus for inventing the Ground Braking Drugs

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Abstract

The Ebola Virus (EBOV) is responsible for the severe and frequently fatal disease known as Ebola Virus Disease (EVD). EVD outbreaks typically begin with a single case of possible zoonotic transmission, which is followed by human-to-human transmission through direct contact or contact with contaminated fomites or bodily fluids. The case fatality rate of EVD is high; it has a fever, symptoms in the Gastrointestinal Tract, and the syndrome of Multiple Organ Dysfunction. Case definition and laboratory tests, typically Real Time Reverse Transcription PCR to detect viral RNA or Immunoassay Based Rapid Diagnostic Tests to detect EBOV antigens, are required for diagnosis. An EBOV-targeted vaccine was recently approved by regulatory agencies in the United States and Europe as a result of recent advancements in medical countermeasure research. The availability of these vaccines are most of the cases impossible specially the arena of developing countries due to their higher cost affectivity. Two monoclonal antibody products that target the EBOV membrane glycoprotein were found to improve survival rates in a randomized clinical trial of investigational therapies for EVD. New strategies for infection prevention and optimization of clinical management, acute illness outcomes, and patient attendance have been developed as a result of new observations made during the unprecedented Western African EVD outbreak (the largest in history) that occurred from 2013 to 2016 and the ongoing EVD outbreak in the Democratic Republic of the Congo. The consequences regarding vaccine technology and its availability, creates a turning of treatment methodologies to invent groundbreaking drugs against this zoonotic virus.

Keywords: Ebola; Zoonotic; Immunoassay; Glycoprotein; Antibodies; Body Fluids

Introduction

Five species belong to the family *Filoviridae's* genus Ebola virus: Ebola viruses from Bundibugyo, Reston, Sudan, Tai Forest, and Zaire are all included. The Zaire Ebola virus, which is more commonly referred to as the Ebola Virus (EBOV) is the primary agent responsible for human outbreaks and the Ebola Virus Disease (EVD). A disease that affects both humans and non-human primates, EVD has a high mortality rate (between 30 and 90 percent). EBOV lives on in the environment in a reservoir animal that has yet to be identified, most likely fruit bats, where it maintains an Enzootic Cycle. Free-tailed bats in Sierra Leone have recently been found to be infected with a new Ebola Virus, the Bombali virus, and Rousettus bats in China have been found to be infected with a new Filovirus, the Menglà virus, both of which lend credence to the role that bats play in the ecology of Filoviruses. In an Epizootic cycle, EBOV can occasionally spread to non-human primates and duikers, resulting in outbreaks with high mortality. In the context of a human-animal interaction, human infection is a sporadic event. Contact with infected human or animal blood or bodily fluids are the primary method of transmission. EVD begins with nonspecific symptoms like fever, fatigue, and muscle pain and progresses to a severe condition with vomiting, diarrhea, irregular bleeding, and mental disorders that eventually lead to coma and death. The convalescence phase of survivors lasts several months and is characterized by memory and appetite loss as well as fatigue and joint pain [1].

The Ebola virus was first discovered in 1976 in South Sudan and the Democratic Republic of the Congo. In humans, this highly pathogenic disease frequently results in death; the case fatality rate in previous outbreaks ranged from 25% (37/149) to 90% (128/143). In the early stages of the disease, symptoms include fatigue, anorexia, vomiting, and diarrhea. Because these symptoms are similar to those of common African Endemic Diseases like yellow fever, malaria, and typhoid fever, it is difficult to diagnose the disease on their own. Early infection mortality is thought to be negatively impacted by factors such as young age, sex, and pregnancy. As a result, it is a viral threat that has significant effects on public health, such as surveillance and treatment of suspected and confirmed cases. Plasma administration has been the mainstay of Ebola treatment. However, there is a high risk of Blood Borne infections being transmitted by this treatment, particularly in African rural areas with limited medical facilities. In this condition, treatment with antivirals like Favipiravir has been successful in extending survival and lowering the viral load. Humanized and Chimeric Monoclonal Antibodies have recently emerged as potential treatments for EBOV. In phase 1 studies, some treatments, like mAb114, REGN-EB3, and BCX4430, demonstrated tolerability and safety; however, their role in treating the acute phase of the disease is unknown [2].

Discussion

Understanding the treatment strategy using drugs is related viral molecular affinity which enhances their mutative nature rather than their molecular structures. Some host factors are important to enhance the bacterial mutative natures. Another important way to change viral infection is to focus on important host factors that are involved in the viral life cycle. Host factors, in addition to being more resistant to mutations than viral proteins, are potential targets for antiviral treatment.

Host targeting agents as influencers

Focusing on important host factors that are involved in the viral life

cycle is another important way to change viral infection. In addition to being more resistant to mutations than viral proteins, host factors are potential therapeutic targets. The AMPK inhibitor compound C is able to prevent EBOV GP-mediated infection of primary human macrophages, which is necessary for EBOV macro pinocytosis in a similar manner, EBOV macro pinocytosis was also inhibited by pyridine imidazole inhibitors of the p38 Mitogen-Activated Protein Kinase (MAPK). Due to its roles in lysosome transportation, host N-Acetylglucosamine-1-Phosphate Transferees (GlcNAc-1-phosphotransferase) was identified as an additional potential EBOV antiviral target. An inhibitor of S1P (cellular proportion converses Sterol Regulatory Element Binding Protein (SREBP) site 1 protease, responsible for the cleavage of the GlcNAc-1-phosphotransferase precursor, PF-429242, was able to block EBOV entry, which requires its GP to be processed in the lysosome, by disrupting GlcNAc- 1-phosphotransferase activity. Another group of potential targets for antivirals are host proteins that facilitate EBOV transcription and translation. The inhibition of Heat Shock Protein 90 (Hsp90) by Geldanamycin, 17-AAG, and Radicicol has been shown to reduce EBOV replication. Hsp90 is an important host factor that is involved in the folding of proteins.

It is also possible to target the proteins involved in viral egress. For instance, viruses frequently hijack TSG101, a housekeeping protein that facilitates the transfer of proteins from the cytosol to the cell membrane. FGI-104, a compound, was found to be a TSG101 inhibitor that prevented mice from being exposed to lethal EBOV and prevented the development of other viruses [3].

EBOV Gene Expression inhibitors

The replication of viruses necessitates viral gene expression, which is dependent on the machinery of the host cell. It has been reported that the EBOV L gene's conserved guanine-rich sequence forms quadruplex RNA, which is then inhibited at the RNA level by the cationic porphyrin TmPyP4. BCX4430, a nucleoside analog, is a viral RNA polymerase inhibitor that has been shown to protect mice from EBOV challenge, which can kill them. Additionally, it has been demonstrated that double-stranded RNA binding protein 76 inhibits the activity of EBOV polymerase.

Nucleotide Analog Pro drug

Gilead Sciences' GS-5734 falls under this category. It is interesting to note that clinical trials have been conducted and the intravenous administration of GS-5734 to the Rhesus monkey inhibited the EBOV's replication. It's also important to remember that this compound can protect against exposure in NHPs [4].

FITR for the N-Terminal Domain of the Ebola Virus Matrix Protein VP40

Seven structural proteins, namely NP, VP35, VP40, GP, VP30, VP24, and L, are encoded in the Ebola virus genome. Since VP40 is the EBOV protein with the highest expression, it is an appealing target for drug design. VP40 is involved in (a) the formation of the virus's filamentous matrix, which defines and maintains the overall shape of the particle, and (b) the budding of EBOV from infected cells. The N-terminal domain of protein VP40 is composed of two domains and has a length of 326 amino acids (1ES6). The C-terminal domain (CTD: residues 1-195 and 196-326).VP40 is able to exist in a variety of conformational states, including hexameric and octameric states, allowing it to modulate its function throughout the virus cycle. The two domains can take on different arrangements in relation to one another.

The question of whether misfolding just one of VP40's two domains would be sufficient to disable the protein's functionality is intriguing. According to experiments and simulations the operation of VP40 necessitates the reorganization of the two domains into distinct conformational states. A hexameric form is the primary component of the virus filament, an octamer structure binds to RNA and regulates transcription, and the protein is transported to the cellular membrane in a generally butterfly-like dimer configuration. These reorganizations are highly dependent on the flexibility of the interactions at the interfaces of the two domains. As a result, it is reasonable to assume that a single domain wide configurationally disruption will likely have significant negative effects on viral functionality [5].

Blocking the entry pathway of virus

It is intriguing to consider whether misfolding just one of VP40's two domains would be sufficient to prevent the protein from functioning. Experiments and simulations suggest that the two domains must be reorganized into distinct conformational states for VP40 to function properly. The protein is transported to the cellular membrane in a generally butterfly-like dimer configuration, an octamer structure binds to RNA and regulates transcription, and a hexametric form is the primary component of the virus filament. The adaptability of interactions at the interfaces between the two domains is crucial to these reorganizations. Consequently, a single domain-wide configurationally disruption is likely to have a significant negative impact on viral functionality, which is reasonable to assume [6].

Simulation of molecular dynamics to better understand how proteins and ligands interact

Although molecular docking can predict the best ligand receptor interactions, not all important interactions between the ligand and the active site of the receptor will be accurately depicted. As a result, molecular docking and MD simulations of the resulting complexes can assist in comprehending interaction modes. Accordingly 196, sulfonamide derivatives successfully bind to the active site of aldose reductase. The experiments showed that these compounds had less activity and binding potential than predicted, so the prediction was false. Later, the key interruption was discovered through MD based in silico refinements of these compounds. In another study MD simulations were used as a platform to discern several different docked complexes of propidium and human acetyl cholinesterase. The most stable structures were identified, which correlated with the experimentally verified binding modes. The reduced activity of these compounds when tested experimentally was explained by the migration of this water molecule from outside.

Homology Modeling for Drug Discovery

In the process of discovering new drugs, protein modeling plays a significant role. The presence of inserts and loop sequences, which cannot be accurately predicted without a Three-Dimensional (3D) crystal structure, is one of the limitations associated with this technique. The gap between known protein sequences and identified protein structures is significantly growing. The goal of homology modeling is to predict a structure from a known sequence with accuracy comparable to experimentally resolved structures. Through a vast array of DNA sequencing, a huge amount of data was given to experimental structure identification techniques require attention. The pharmaceutical industry actively uses computational methods for the prediction of 3D protein models. Continuous efforts are being made to improve model accuracy and broaden the scope of computational methods. To address

Citation: Ground E (2023) Molecular Strategies of Ebola Virus for inventing the Ground Braking Drugs. Air Water Borne Dis 12: 168.

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this problem, these methods assist in predicting a protein's tertiary structure based on its amino acid sequence [7].

Significance of Drug Therapy over Vaccine Technology

The development of therapeutic antibodies and small molecule inhibitors that protect nonhuman primates from EBOV challenge is a major milestone as is advancement of therapeutics into clinical trials. Given that none is yet approved for human use and the facts that propensities of these approached to elicit resistance, continued efforts at drug development for filo viruses remains a necessity. Small molecule approaches targeting conserved viral functions would seem to offer the greatest possibility for Filo virus efficacy [8].

The RNA vaccinology field is continually advancing as new examinations plan to work on in vitro record, streamline adjuvant and conveyance plans, and eventually refine in vivo pharmacokinetics. However with such a huge variety in immunization draws near and not very many equal comparisons, it is hard to unravel which procedures are ideal. Laying out clinical adequacy is the following significant stage but it's developing. Cost affectivity and in adequacy of proper clinical trials lead to almost impossible to continue treatment strategy using vaccine technology specifically in case of under developed countries [9].

Conclusion

After the largest and most devastating Ebola outbreak in history, EVD treatment efforts have gained significant significance. The urgency of developing an effective treatment that can be used to prevent future outbreaks has been highlighted by this outbreak. Numerous countermeasures, including vaccines, have been developed as a result of clinical research. To ensure a licensed, effective drug for future outbreaks, the scientific community must overcome multiple obstacles. In light of this, it is necessary to broaden the possibilities for the creation of therapeutic agents that have broad-spectrum activity against filo viruses like pathogens. However, the drug discovery and development pipeline only results in a small number of compounds that are put through clinical trials, making the process not only difficult but also time-consuming [10].

Acknowledgement

None

Conflict of Interest

None

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