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Mini Review

Drug Discovery in the Ebola Virus

Elena Daniel*

Department of Pharmacology and Therapeutics, Australia

*Corresponding Author's E-mail: danielelena@rediff.com

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Abstract

Rare and fatal, Ebola virus disease (EVD) affects both humans and nonhuman primates. EVD-causing viruses are primarily found in sub-Saharan Africa. Direct contact with an infected animal (such as a bat or nonhuman ape) or a sick or deceased person who has the Ebola virus can cause EVD in humans (Huang et al., 2014).

One of the most catastrophic transmissible diseases, Ebola Virus Disease (EVD) is brought on by a member of the Filoviridae family and is one of the most deadly infections that can be transmitted. The recent severe EVD outbreak in Western Africa (2013–2016) brought to light the disease's global threat as well as its effects on public health and the economy. The lack of resources to investigate the Ebola virus's life cycle in vitro and screen for potential active compounds outside of a biosafety level-4 (BSL-4) confinement has so far impeded the development of vitally required anti-Ebola virus antivirals. Importantly, the creation of surrogate models, such as viral pseudotypes and Ebola virus-like particles, to study Ebola virus entry in a BSL-2 environment has significantly improved our understanding of the viral life cycle and led to the discovery of promising antiviral compounds that block viral entry. In this regard, the use of such surrogate systems in conjunction with large-scale small molecule compounds, haploid genetic screens, rational drug design, and drug repurposing approaches will prove invaluable in our quest to create a treatment for EVD (Williams 2003).

Keywords: Ebola virus, Filoviridae, vsv, Retroviral vectors, Virus-like particles, Pseudovirus, antivirals, Small molecules, Viral entry

INTRODUCTION

Ebola virus sickness is a serious and frequently fatal illness brought on by Ebola viruses (EVD; previously referred to as Ebola haemorrhagic fever). Up to 90% of cases during EVD epidemics end in death. Haemorrhagic fever is a disorder that may be caused by other viruses as well, but Ebola viruses generate one of the most deadly versions. The more severe cases of haemorrhagic fever can also include blood vessel destruction and significant internal and external bleeding in addition to the other symptoms of the condition, which can include fever, headache, muscular pain, weakness, vomiting, and diarrhoea (haemorrhage). The mortality rate with EVD is between 25% and 90%, with an average of 50%. Death typically results from shock brought on by fluid loss rather than blood loss. Although novel therapies and vaccinations are being investigated, there are currently no authorised medications or vaccines to treat EVD (Dahlin et al., 2004). The amount of initial viral exposure, the timing of therapy initiation, the patient's age, and the patient's immune response all appear to have an impact on recovery. Early supportive treatment, such as maintaining bodily fluids and electrolytes and monitoring blood pressure, can increase survival chances and give the body's immune system more time to fight off the infection. Younger folks seem to heal more quickly than elderly people. When people recover, they produce antibodies that might remain for at least ten years. Long-term consequences in some survivors include joint and eye issues (Kreda et al., 2001).

A wide range of scientific disciplines, including physical, chemical, biological, bioinformatics, and medical ones, are used in the field of molecular medicine to describe molecular structures and mechanisms, pinpoint the underlying molecular and genetic flaws that cause disease, and create molecular interventions to correct them. Instead

of the earlier conceptual and observational focus on patients and their organs, the molecular medicine paradigm places more emphasis on cellular and molecular events and interventions (DeMaio et al., 2009).

In the process of developing cardiovascular drugs, non-invasive imaging has become more and more important. This review focuses specifically on the use of molecular imaging, which has been used more frequently to advance and speed up a number of preclinical drug development steps, such as the selection of appropriate therapeutic targets, the assessment of the on- and off-target effects of potential treatments, the evaluation of dose response, and the assessment of drug or biological bio-distribution and pharmacodynamics. Molecular imaging has not been employed as a main surrogate clinical end point for medication approval in cardiovascular medicine, in contrast to the situation in cancer medicine. However, to prove the notion or to explain variation in treatment impact, molecular imaging has been used in early clinical trials, particularly in phase 0 research. Numerous of these uses of molecular imaging in drug development required the repurposing of tools that were designed with clinical diagnosis in mind. With more practise and understanding of the wealth of data that in vivo molecular imaging offers, it is hoped that it will be utilised more frequently to address the significant time and expense involved in bringing a new medicine to the clinical launch stage (Newman et al., 1999).

The processes of drug discovery and incremental drug development have been accelerated to the point of clinical launch thanks to recent advances in applied molecular biology. The development of high-throughput technologies for quick and automated candidate molecule screening, the pharmaceutical application of omics approaches to comprehend the underlying mechanisms of targets related to health and disease, and the use of virtual screens for understanding structure have all contributed to the acceleration of drug discovery. However, the healthcare sector is today dealing with unheard-of barriers to the creation of truly novel treatments. The erosion of faith in pharmaceutical corporations due to actual or perceived failures in commercial ethics, scientific rigour, and scientific reporting is one issue that has grown more and more obvious through media outlets. It is unlikely that these issues will be resolved just by the scientific community (Liou et al., 2013).

The business paradigm that underpins drug research and preclinical and clinical testing presents an equally significant challenge. The percentage of approved pharmaceuticals that are considered first-in-class or new molecular entities has steadily decreased over the past 20 years, mostly for financial reasons. Over the past ten years, cancer treatments and biologics have accounted for the bulk of first-in-class medicines, having less of an influence on cardiovascular disease than cancer, inflammatory, or rheumatologic diseases (Siniscalco et al., 2008).

The practise of cardiovascular drug testing has become more and more dependent on non-invasive imaging. The evaluation of left ventricular function, pulmonary artery pressure, myocardial ischemia, and arterial morphology (e.g., plaque size by intravascular ultrasound) are just a few concrete examples of biological readouts that have been assessed by conventional imaging in preclinical models and humans. These measurements have each been used in preclinical and clinical studies to assess drug efficacy or to provide proof-of-mechanism information crucial to drug approval. For virtually all types of non-invasive in vivo imaging, more recent molecular imaging methods have been developed that can describe tissue phenotype. Their creation is predicated on the idea that by offering (1) an earlier diagnosis, (2) a more certain diagnosis, and (3) information useful for choose the best treatment, they will enhance patient outcomes and healthcare effectiveness. This article's main argument centres on how non-invasive in vivo molecular imaging may boost the effectiveness of getting a medicine approved at various phases of development (Tzouvelekis et al., 2013).

DISCUSSION

Five species make up the genus Ebolavirus, which belongs to the family Filoviridae: the Bundibugyo, Reston, Sudan, Tai Forest, and Zaire ebolaviruses. One of them, the Zaire ebolavirus, also known as the Ebola virus (EBOV), is the primary cause of human epidemics and the disease caused by the Ebola virus (EVD). The disease EVD, which affects both humans and non-human primates, is known for its high mortality rate (30–90%). The fruit bat is the most likely animal reservoir where EBOV survives in the environment and is kept in an enzootic cycle. Recent discoveries of a new ebolavirus, the Bombali virus, in free-tailed bats in Sierra Leone and a new filovirus, the Mnglà virus, in rousettus bats in China emphasise the importance of bats in filovirus ecology. On rare occasions, EBOV can spread to duikers and non-human primates during an epizootic cycle, resulting in epidemics with a high fatality rate. An incident involving human infection that occurs at a human-animal contact is sporadic. Contact with blood or a bodily fluid from sick people or animals is the primary means of transmission. EVD starts with vague symptoms like fever, exhaustion, and muscular aches and progresses to a serious condition with symptoms like vomiting, diarrhoea, infrequent bleeding, and mental instability that eventually results in a comatose state and death. Survivor patients go through a convalescence period that lasts many months and is characterised by exhaustion, joint discomfort, loss of appetite, and memory loss. Long after symptoms have subsided, viral RNA can still be found in some tissues, such the testis (Ghaedi et al., 2013).

Up until 2014, EVD was regarded as a disease that was being ignored and caused isolated outbreaks in African villages. Due to its possible use as a bioweapon, EBOV study was restricted to a small number of laboratories with biosafety

level-4 (BSL-4) facilities and was mostly focused on biological aspects of viral infection or preparedness. However, the most recent significant EVD outbreak (Western Africa, 2013–2016), marked by 28,616 cases and 11,310 fatalities, brought to light the disease's widespread risk as well as its effects on the economy and public health around the world. In order to create efficient preventive and therapeutic methods, research on the molecular dissection of the EBOV life cycle received tremendous encouragement and financial assistance. In this study, we provide an overview of what is currently known about one particular stage of the EBOV life cycle, entrance, the substances that have been shown to be able to interfere with it thus far, as well as the molecular models that were employed for these goals.

CONCLUSION

People usually get cases of EVD after handling and slaughtering these sick animals. Once the virus has infected humans, it may swiftly travel from person to person among family members and other intimate contacts, as well as among patients in medical facilities. To stop widespread epidemics, it is essential to identify cases quickly. Molecular target-based drug discovery has increasingly taken the position of traditional natural product-based drug discovery, which involved extraction, assay-based functional fractionation, isolation, characterization, and target validation. Over the past two decades, high-throughput screening of vast compound libraries, including computer-based in silico screening, lead identification from hits, in silico docking analysis of protein X-ray crystal structures, and lead optimization have become common practises. To date, only one FDA-approved drug (sunitinib for renal carcinoma) has come from high-throughput screening of combinatorial chemistry libraries, followed by the optimization of hits. This is in contrast to the simple random high-throughput screening of a sizable number of small molecule libraries generated by combinatorial chemistry. As a result, natural product-based medications (parent compounds, derivatives, analogues, and mimics) continue to make up a significant portion of FDA-approved medications (57.7% of all medications). Nevertheless, many drug discovery and development situations have seen success using combinatorial chemistry in the form of parallel synthesis or diversity-oriented synthesis (DOS) for the optimization of extremely promising lead compounds. For meeting ADME/Tox (absorption, distribution, metabolism, excretion, and toxicology) standards, the concentrated library method is extremely helpful.

The creation of efficient anti-EBOV therapies is one of the top public health priorities due to the ongoing recurrence of EVD outbreaks in Africa and the possible risk of epidemics spreading to other continents as well as the potential for using EBOV as a bioweapon. Our understanding of filovirus entrance and the discovery of potential, desperately needed antivirals were both advanced by the establishment of BSL-2 restricted systems to research the entry of such highly dangerous viruses outside the BSL-4 facilities. A variety of chemical structures are made available for further modelling and research of the relationships between structure and activity as a result of the optimization of screening techniques at the miniaturised scale. Additionally, by combining various models, it is possible to analyse the stages of the viral replication cycle that drug candidates affect, providing insight into the mode of action of prospective novel antivirals. Although utilising such viral models helps hasten the discovery of drugs that are effective against EBOV, it is crucial to confirm the findings using the real virus, especially for drugs that have a direct effect on GP. In reality, due to the role that soluble GPs play as a decoy, the synthesis of significant amounts of soluble GP forms by the original virus can affect the effectiveness of the antiviral activity. It is also possible to determine whether several cellular targets contribute to the antiviral efficacy in the case of drugs that affect host cell functions, as is the situation when a medication repurposing method is used. These details could be used to alter the compounds under consideration and enhance their antiviral effectiveness while reducing any negative consequences. Given EBOV's high pathogenicity and viruses' propensity for developing medication resistance, research into novel compounds that target several viral or host components ought to make it possible to create effective antiviral combinations. In this regard, both in vitro and in vivo investigations have shown evidence of the synergistic effects of medication combinations. Last but not least, the recent surge in anti-filo viral research could aid other infectious diseases that have gone untreated by producing a wide array of medications that can be utilised to manage outbreaks brought on by other viral agents.

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