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Research Article

Structure based virtual screening of the Ebola virus trimeric glycoprotein using consensus scoring

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ABSTRACT

Ebola virus (EBOV) causes zoonotic viral infection with a potential risk of global spread and a highly fatal effect on humans. Till date, no drug has gotten market approval for the treatment of Ebola virus disease (EVD), and this perhaps allows the use of both experimental and computational approaches in the antiviral drug discovery process. The main target of potential vaccines that are recently undergoing clinical trials is trimeric glycoprotein (GP) of the EBOV and its exact crystal structure was used in this structure based virtual screening study, with the aid of consensus scoring to select three possible hit compounds from about 36 million compounds in MCULE's database. Amongst these three compounds, (5R)-5-[[5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl]methyl]-N-[(4-methoxyphenyl)methyl]-4,5-dihydroisoxazole-3-carboxamide (SC-2, $C_{21}H_{19}ClN_4O_4$) showed good features with respect to drug likeness, ligand efficiency metrics, solubility, absorption and distribution properties and non-carcinogenicity to emerge as the most promising compound that can be optimized to lead compound against the GP EBOV. The binding mode showed that SC-2 is well embedded within the trimeric chains of the GP EBOV with molecular interactions with some amino acids. The SC-2 hit compound, upon its optimization to lead, might be a good potential candidate with efficacy against the EBOV pathogen and subsequently receive necessary approval to be used as antiviral drug for the treatment of EVD.

1. Introduction

Ebola haemorrhagic fever in humans, often called Ebola virus disease (EVD), is a serious illness caused by deadly Ebola virus (EBOV). Although the popular EVD outbreak in history was recently witnessed between 2014 and 2016 in West African countries such as Liberia, Guinea, and Sierra Leone (Choi et al., 2015; Bah et al., 2015; WHO, 2016a), its first outbreak was recorded simultaneously in Yambuku area of Democratic Republic of Congo (DRC) and Nzara region of South Sudan in 1976 (WHO, 1978; Feldmann and Geisbert, 2011; Grard et al., 2011). The West African epidemics was caused by a particular species of EBOV called *Ebolavirus zaire* (Bah et al., 2015; Weyer et al., 2015; CDC, 2016) and this deadly species, like others in the Filoviridae family, replicate adeptly to spread easily in monocytes, fibroblasts, macrophages, adrenal gland cells, dendritic cells and other cells (Ansari, 2014). The viral replication activates high-level release of inflammatory chemical signals that overwhelms the host immune defenses to cause a diseased state (Tosh and Sampathkumar, 2014).

Countries like Spain, USA and some other African countries later experienced EVD and the spread made the World Health Organization (WHO) to initially declare the outbreak to be of international public health emergency in 2014 (WHO, 2016b). Aside the recorded death, the EVD scourge affected socio-economic sectors of the aforementioned three West Africa countries, to the projection of $2.2 billion as their gross domestic product (GDP) loss in 2015 (World Bank, 2014). Perhaps, this great loss motivated the global donation of $3.611 billion for the establishment of international Ebola response and Emergency Operations Centers in those affected West Africa countries (USAID, 2015). Meanwhile, the transitory success recorded in managing the EVD nuisance possibly made WHO, in March 2016, to revoke the

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earlier pronouncement of EVD as of international public health emergency. It, however, became worrisome as there was resurgence of the epidemic in May 2017 in DRC (WHO, 2016b) and this resurgence further called for improved efforts towards curtailing its potential scourge.

Both genomic and epidemiological analyses suggest a single zoonotic transmission event prior to man-to-man transmission (Gire et al., 2014). Specifically, the fruit bats and non-human primates such as monkey, chimpanzees, gorillas, etc. primarily transmit the EBOV to man and this further spreads through man-to-man transmission via direct contact with any bodily fluids of infected animal or man (Funk and Kumar, 2014; Drazen et al., 2014. Humans only become infectious with the appearance of some symptoms similar to those for other common diseases. Similarity of symptoms may be responsible for the late identification of EBOV infections (Ye and Yang, 2015). Early symptoms of EVD include sore throat, headache, muscle pain and fever fatigue, while rashes, vomiting, internal and external bleeding, impaired kidney, diarrhea, etc constitute the later symptoms of the infection (Hoenen et al., 2006; Ohimain, 2016; Hartley et al., 2017).

Successful control of EVD outbreaks entails public awareness of risk factors of the infection as well as protective measures such as vaccination and rapid supportive care with rehydration (WHO, 2017). Quite a number of therapeutics or vaccines have been evaluated to be successful in animal model and are presently on human trials (Stanley et al., 2014; Henao-Restrepo et al., 2015; Tapia et al., 2016; Ledgerwood et al., 2017), but no one has been able to secure required approval to be used for the EVD treatment. Thus, there are continuous efforts towards identifying most viable antiviral drug against EBOV through research outcomes from academic and pharmaceutical industries. Undoubtedly, exorbitant and lengthy processes are involved in discovering a new drug. Tufts Center for the Study of Drug Development recently estimated an average cost of $US 2.558 billion and about 15–20 years for the development of a new drug and procurement of its market approval (Ashburn and Thor, 2004; DiMasi et al., 2016). However, computational modeling proffers a faster, cheaper, and reliable approach to the current drug discovery processes and it minimizes animal testing in the processes (Kapetanovic, 2008).

Interestingly, virtual screening reduces the computational sampling space to make computational calculations more tractable. Most recent reports on virtual screening against EBOV used small database of screened compounds and/or homology models of the EBOV glycoproteins (Veljkovic et al., 2015; Raj and Varadwaj, 2016; Ahmad et al., 2017). For instance, Ahmad et al. (2017) conducted molecular simulation and docking study of the EBOV GP using homology modeling techniques to speculate dronedarone and amiodarone as potential glycoprotein receptors. It is noteworthy that homology model gives a lower resolution than the exact protein structure and depends on model quality (Al-Karadaghi, n. d.), and so it is not satisfactory to use homology model when the exact protein structure from a pathogen is known. Furthermore, identifying the crystal structures of the secreted glycoprotein is necessary to find active sites in the process of receptors designing. The trimeric glycoprotein (GP) has been identified as the main target of potential vaccines that are presently undergoing clinical trials (Stanley et al., 2014; Henao-Restrepo et al., 2015; Tapia et al., 2016; Ledgerwood et al., 2017). Moreover, the use of consensus scoring concept significantly advances the virtual screening performance as it improves the prediction of bound conformations and poses, and gives a better prediction of potential leads (Feher, 2006). The benefits of consensus scoring make it a good choice in this in silico study and the exact trimeric glycoprotein (GP) crystal structure of the EBOV is employed to investigate potential hit compounds with yearning efficacy upon optimization, if necessary, against the EBOV pathogen and subsequently secure necessary approval to be used as antiviral drug for the treatment of EVD.

2. Methodology

2.1. Target protein preparation

Target selection is an important step and its correct choice is crucial to the success of drug discovery (Bunnage, 2011; Bunnage et al., 2015). The choice of target protein in this study is borne out of the fact it is the main target of potential vaccines that are undergoing clinical trials (Stanley et al., 2014; Henao-Restrepo et al., 2015; Tapia et al., 2016; Ledgerwood et al., 2017). The trimeric viral surface glycoprotein of the EBOV (PDB ID: 5KEN) prepared with the use of cryo-electron microscopy (Pallesen et al., 2016) was downloaded from the protein databank (Berman et al., 2000) and employed as target protein in the virtual screening experiment Fig. 1. The antibodies attached from the downloaded structure were removed to avoid any unwanted molecular interaction with the target protein during the virtual screening using Discovery studio (Biovia, 2015). The good quality of the glycoprotein was validated using Ramachandran plot (Fig. 2). The grids which include the binding center and dimensions were calculated using the PyRx program (Dallakyan and Olson, 2015). The binding center has 159.7348, 159.9271 and 156.0968 as coordinates for X, Y and Z axes respectively while the binding dimension in Angstroms were 208.6559, 199.6780 and 196.8750 for the X, Y and Z axes respectively. The binding parameters used ensured that the whole target protein was enclosed in the grid.

2.2. Ligand preparation and virtual screening

The Mcule database (Kiss et al., 2012), consisting of exactly 35,742,734 compounds as at the time of conducting this work, was used for the virtual screening experiment. The compounds were filtered using the same parameters as earlier reported to ensure that selected compounds have good physicochemical drug like properties (Onawole et al., 2017). Auto Dock Vina (Trott and Olson,

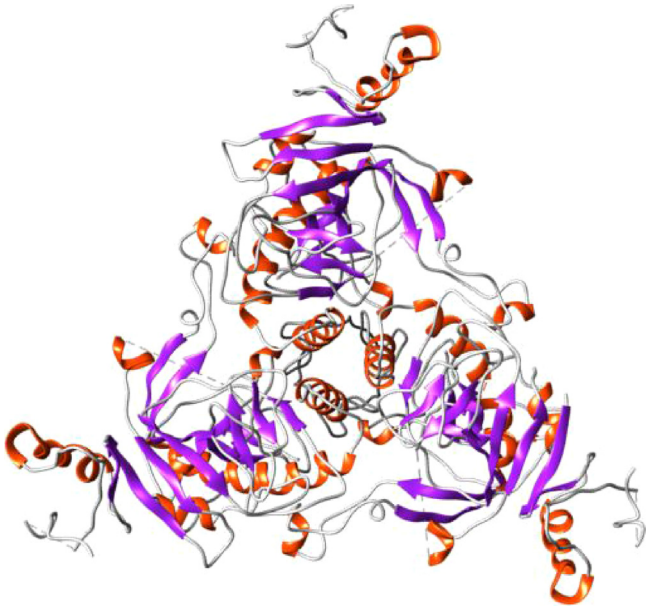

Fig. 1. Structure of the trimeric viral surface glycoprotein of the Ebola virus (EBOV). *–β sheets–purple, α helices–brown, loops and turns–white. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)