Chapter 8

Strategies for the Development of Small Molecule Inhibitors of Ebola Viral Infection

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Additional information is available at the end of the chapter

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Abstract

The recent outbreak of Ebola viral disease (EVD) in West Africa reminded us that an effective anti-viral treatment still does not exist, despite the significant progress that has recently been made in understanding biology and pathology of this lethal disease. Currently, there are no approved vaccine and/or prophylactic medication for the treatment of EVD in the market. However, the serious pandemic potential of EVD mobilized research teams in the academy and the pharmaceutical industry in the effort to find an Ebola cure as fast as possible. In this chapter, we are giving the condensed review of different approaches and strategies in search of a drug against Ebola. We have been focusing on the review of the targets that could be used for *in silico*, *in vitro*, and/or *in vivo* drug design of compounds that interact with the targets in different phases of the Ebola virus life cycle.

Keywords: small molecule inhibitors, Ebola virus, drug design, protein targets, structure and action

1. Introduction

Ebola virus (EBOV) is a (-)ssRNA filovirus, known for its extreme insidiousness. Case fatality rates of the current 2014 outbreak in West Africa are 50–70% [1]. Transmission of EBOV is predominantly via physical contact with bodily fluids of infected people or corpses and can be limited by a proper combination of early diagnosis, contact tracing, isolation of patients, infection control, and safe burial [2, 3].

The infection is characterized by suppression of the immune system and of the systemic inflammatory response, followed by the collapse of the vascular and immune systems, and

multi-organ failure. The patient dies from a combination of dehydration, massive bleeding, and shock. Currently, there are no approved drugs for the hemorrhagic fever caused by EBOV. However, there is some conflicting clinical evidence that antibodies isolated from survived patients may be effective in the treatment of the infection caused by EBOV [4, 5].

In this book chapter, we will review possible targets that are being used or could be used for structure-based design of small molecule inhibitors against EBOV. We will start the chapter with a brief review of the structure and action of EBOV, and then we will describe the targets along with possible hotspots. Additionally, we will present a short review of small molecules that could be used as medicaments against EBOV.

2. Structure and action of Ebola virus

Knowledge about the life cycle of EBOV, supported with structural information, is crucial for the successful design of antivirals. This is the reason why we will start our review with the structural information about EBOV.

The RNA genome of Ebola virus contains information for constructing seven proteins (GP, VP24, VP30, VP35, VP40, L-protein, nucleoprotein), which assemble with the genomic RNA to form one of the most lethal viruses [6]. EBOV's RNA exists in antisense form, which means that it cannot be used for proteins' production directly [7]. For protein building, the complementary copy of the negative RNA is required, which is produced with the help of the viral polymerase (L-protein). Not all genes are transcribed fully through. For example, transcription of GP gene could lead to three different proteins: GP, sGP, and ssGP. A small nonstructural sGP (secretory glycoprotein) is the protein that is efficiently secreted from infected cells. sGP acts as mimic of full GP that is presented at the surface of EBOV, this mimicry is one of the ways of how the Ebola virus deceive the immune system, by urging the body to develop antibodies to sGP instead of full GP [8, 9]. EBOV is enclosed by a membrane hijacked from an infected cell and covered with Ebola glycoproteins. A layer of matrix proteins supports the membrane on the inside and holds a cylindrical nucleocapsid at the center, which stores and delivers the RNA genome.

The main task of Ebola glycoprotein (GP) is binding to receptors located on a host-cell surface and getting the Ebola genome inside. GP is distributed throughout the whole viral membrane surface and the large proportion of oligosaccharides, which are attached to the GP making the virus unrecognizable for the adaptive immune system. GP is a highly dynamic protein that snaps into different shapes when it binds to a cell surface, driving the virus close enough to get fused with the membrane.

The viral matrix is composed of two proteins: VP40 and VP24. The function of VP40, known as the major matrix protein, is to assist in the process of budding. VP40 hexamers form layers that support the nucleocapsid in the middle of the virion. The minor matrix protein VP24 is involved in interferon antagonism.

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