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Molecular Aspects of Creating Therapeutic and Vaccine Strategies against Ebola Virus Disease

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Abstract

The disease caused by the Ebola virus is an exceptional danger to public health due to the high mortality rate combined with the actual absence of antiviral therapy and an effective vaccination algorithm, as well as the main pathogen of the biological threat of the highest category. This state of affairs explains the inclusion of The disease caused by the Ebola virus in the list of diseases covered by the International Health Regulations of 2005. Both the epidemic of 2014-2015 and the real pandemic with VID-19 showed the exceptional inadequacy and unpreparedness of the world health care for such a large-scale disaster. The relevance of this topic lies in the consideration of this problem through the analysis of the experience of the Ebola epidemic and the construction of correlations with today's pandemic.

Disciplinary: Medicine.

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1 Introduction

It is well established that filoviruses block the immune response of the body and protect the cells in which they replicate [1]. Infected cells emit a huge amount of chemokines and cytokines,

which include interleukins and interferons, thereby triggering cascades of procoagulant protein tissue factor, which disrupts blood clotting and damages blood vessels [2].

In the early stages, inflammatory factors appear in the form of an increase in the total number of cytokines, such as IFN-α, IL-6, macrophage inflammation proteins. In the later stages, IFN-β and INF-γ, IL-18, nonspecific inflammatory factors characteristic of such dangerous infections as plague or tularemia, and others appear [3-7]. Inflammatory cytokines act systemically, inducing a characteristic clinic. In high concentrations, they are extremely toxic. They are able to start a chain of phenomena: general coagulation, release of IL-6, NO (nitric oxide) and TNF-α, violation of vascular integrity and homeostasis [8].

The study of the effect of the Ebola virus on the interferon system showed a significant variety of options for suppressing the antiviral response induced by them [9]. Ebolovirus is a heavy inducer of IFN-α formed in leukocytes. In turn, fibroblasts, in response to antigens, begin to produce β-IFN, and T-lymphocytes – interferon type γ. These cells are damaged as a result of the introduction of ebolavirus, so when viruses disrupt the cellular mechanisms of induction of IFN-dependent genes, acting on the activation of signaling factors of the STAT transcription, they can have virtually no response [10]. The viral proteins mentioned above begin to interact with tyrosine kinases and interfere with phosphorylation. As a result, there is a solid block of activity of the IFN system at the stage of signaling to antiviral cell genes, thereby providing all the conditions for viral reproduction. The induction mechanism involves interferon-regulated endogenous factors and Tool-like receptors. RNA genomic viruses interact with Tool-like receptors on the surface of cell membranes. Signal kinases and RNA helicases are involved in the induction of IFN formation, directing signals to IFN-regulated endogenous factors. What is important: receptors for IFN are associated with tyrosine kinases that activate latent transcription factors, namely STAT-1 and STAT-2. As a result: there is an induction of transcription of IFN-dependent genes of antiviral proteins. Biochemical processes of antiviral action include selective suppression of transcription and translation of viral genome molecules in affected cells using various enzymatic systems [11-15].

Interferons are important cytokines that control the development of viral infections. The known types of human interferons are divided, as it is known, into two types: leukocyte and fibroblast profile. Ebola virus is induced by type I (leukocyte) IFN. And although, despite the fact that this virus suppresses the production of interferons in the microorganisms, at the same time, they have a rather strong sensitivity to the action of IFN in the preventive scheme of use. The effectiveness of antiviral action, by the way, is significantly reduced if IFN drugs are administered after viral infection [16-18]. But this will be discussed in detail later.

As noted above, knowledge of the biochemical foundations of the structure and replication of ebolaviruses, as well as the principle of blocking their production of interferons, allows us to develop ways to treat these infections and, first of all, the disease caused by the Ebola virus [19].

The purpose of this work is to describe the molecular mechanisms of protection of human immunity and to analyze the most promising methods of therapeutic strategy against the Ebola virus from the modern articles proposed in the system.

2 Literary Review

This study was conducted taking into account the analysis of various literature data published no later than the last 5 years. From the analysis it was found out that the existing methods of therapy include the use of interferon-α, heparin, specific antiviral immunoglobulins of horses and serum obtained from convalescents.

A relatively new technology of RNA interference allows in vitro to suppress the expression of the target target gene using short double-stranded RNAs up to 23 nm long, and having, moreover, the same sequence as the mRNA that was previously transcribed from the target gene. The ultimate target for interfering RNAs is the RNA-dependent RNA polymerase, i.e. the L-protein of the Ebola virus [20].

The use of antisense oligonucleotides, the principle of which is used in therapy in cancer patients, is also shown. In the case of the disease caused by the Ebola virus, various combinations of antisense phosphorodiamidate-morpholine-oligomers are used. These molecules are aimed at retarding Ebola virus replication in cells [21].

And although the work on creating a cure for the disease caused by the Ebola virus is being carried out intensively, so far none of the available drugs is able to provide reliable protection from infection. Although the principle of pathogenetic therapy is fully understood and accepted: the fight against hemorrhagic and DIC syndromes, HIV prevention, relief of intoxication and hemocoagulation [22,23]. It is also important to increase the immunospecific resistance of the macroorganism in order to prevent the appearance of associated infections [24]. By the way, freshly frozen plasma is used for this (preferably convalescents; for shock relief – hemodilution method); large doses of vitamins C, D, P, group B; vascular analeptics; fluoroquinolone antibiotics for the prevention of opportunistic infections and painkillers [25-27]. Next, we will talk about the most relevant and promising developments in the field of vaccination.

3 Current and Promising Developments in the Field of Vaccination

Not so long ago, the creation of vaccines against filoviruses was of no commercial interest. This was due to the fact that the area of escalation of this group of diseases was very limited. And, of course, the Ebola virus outbreak was a turning point in the entire pharmaceutical system. Obviously, the interest arose not only because of the natural wave of epidemics. Many seriously fear that filoviruses can be used as bioterroristic weapons of mass destruction. Therefore, a universal vaccine is necessary, first of all, for medical personnel working in the foci of the disease, the military and researchers.

To date, an effective strategy for the development of vaccines is the methods of reverse genetics, when other viral particles are used as the main carrier of the "vector" of the vaccine [28].

The most successful options are adenovirus, vesicular stomatitis virus and parainfluenza virus. During the study of this topic, it was decided to expand the concept of a second Canadian-made vaccine with vesicular stomatitis virus.

The vaccine was named "V920" (rVSV-ZEBOV) and was successfully used in animal experiments. Its essence lies in the fact that recombinant viruses are able to replicate in the host body, but are not detected in biological fluids and do not show any clinic. Endogenously, in the body, they are "examined" by the dendritic cells of the macroorganism and, thus, the primary information signaling of immunity is produced in case of penetration of ebolavirus.

Thus, based on the knowledge gained about the molecular and biochemical aspects of the Ebola virus, a number of promising vaccines based on various viral vectors have been developed in recent years, which have proven positive dynamics in animals. At the same time, additional studies are required to confirm the safe use of such in humans.

4 Conclusion

Despite the full-fledged shifts in the study of the disease caused by the Ebola virus and the Ebola virus, they pose an exceptional danger to public health due to the high mortality rate combined with the actual absence of antiviral therapy and an effective vaccination algorithm.

In the course of this work, the chronological order of the main events related to ebolavirus in the XX-XXI centuries was considered; aspects of the occurrence, spread and clinical manifestation of the disease caused by the Ebola virus were studied.

An important task was to show why the mortality rate and the risk of infection with Ebola viruses are extremely high, so most of the work was devoted to this issue. At the level of molecular processes, it was considered how ebolavirus penetrates into the target cells of the host, its replication, and escalation throughout the body. In order to demonstrate the relevant data, a goal was set and fulfilled with the disclosure of the question of the etiology and biochemical structure and functioning of the virus.

An analysis of the current developments of the world medical community makes it clear that, in general, methods and actions aimed at therapy, prevention and vaccination of the population against the disease caused by the Ebola virus have existential prospects for use already in the present. It remains only to continue the evolution of the pharmaceutical campaign in achieving safe and effective drugs for humans [29-30].

5 Availability of Data and Material

Data can be made available by contacting the corresponding author.

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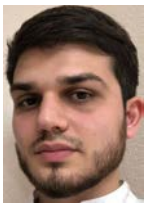

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