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The Role of Endothelial Cell Dysfunction in Hemorrhagic Fevers

Ciamak Ghazaei[1*]

[1]Department of Microbiology, University of Mohaghegh Ardabili, Ardabil, Iran

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***Correspondence to**
Ciamak Ghazaei,
Email:ciamakghazaei@yahoo.com

Abstract
Endothelial cells (ECs) that line the inner surface of blood vessels play a crucial role in maintaining healthy blood vessels and regulating consistent blood flow. EC dysfunction (ECD) is the improper functioning of ECs as a result of any modification or damage. Numerous health issues such as cardiovascular disease, hypertension, lightheadedness, exhaustion, diabetes, and the like could result from this. Both extrinsic and intrinsic factors may cause ECD. Many virus-induced hemorrhagic fevers, including dengue fever, Ebola, and Lassa fever, exhibit ECD. ECs maintain barrier functions by regulating immune cell interactions, homeostasis, and capillary permeability, and in viral infections, viral interaction alters these factors. These pathogens destroy ECs, leading to a loss of integrity in the blood vessels and increased permeability. Hemorrhagic fever can cause a wide range of symptoms such as fever, headache, muscle pain, weakness, exhaustion, bruises, bleeding, shock, and occasionally even the emergence of additional issues such as organ failure. Hemorrhagic fevers can be life-threatening if not treated promptly and correctly. Considering that ECD can be a silent condition, consultation with physicians about individuals' risk factors and regular screenings to detect and prevent this condition is highly important. There is no specific antiviral treatment for most hemorrhagic fevers, but research is ongoing to develop effective treatments. This review will discuss the ECD due to viral interactions to cause hemorrhagic fevers, available treatments, and challenges associated with such viral hemorrhagic fevers (VHFs).
Keywords: Endothelial cell, Dysfunction, Hemorrhagic fevers, Pathogenesis

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Introduction

Hemorrhagic fevers are a group of severe and often life-threatening diseases caused by various viruses, including the Ebola, Marburg, and Lassa fever viruses.[1,2] These illnesses pose a serious risk to the public's health due to their propensity for excessive bleeding and high fatality rates. One of the key features of hemorrhagic fevers is the disruption of the normal functioning of the body's endothelial cells (ECs), which line the inner surface of blood vessels. EC dysfunction (ECD) is thought to be a key factor in the development of the severe bleeding detected in these diseases.[3] ECs play a crucial role in maintaining healthy blood vessels and regulating consistent blood flow. To ensure proper oxygen and nutrient delivery to tissues and organs, waste should be removed from the body, body temperature must be regulated, organ function should be maintained, and the formation of blood clots must be prevented, which can cause a heart attack and a stroke, healthy blood vessels, and consistent blood flow are essential.[4]

With the emergence of numerous infectious diseases, particularly mutant viruses that frequently result in hemorrhagic states, researchers have recently grown more interested in understanding how ECD contributes to the pathophysiology of hemorrhagic fevers.[5] Viral hemorrhagic fevers (VHFs) are zoonotic diseases that have poor diagnosis during infections, lack good preventive and curative measures such as drugs and vaccines against them, resulting in high mortalities.[6] Therefore, the knowledge of viral pathogenesis mechanisms is essential to find good therapeutic choices to treat such VHFs. This review will provide a comprehensive overview of the current state of knowledge on the mechanisms of ECD in hemorrhagic fevers and discuss its potential implications for the development of new treatments for these diseases. It will also explore the current challenges and limitations in understanding the mechanisms of ECD in hemorrhagic fevers and outline areas for future research.

Hemorrhagic Fever

Hemorrhagic fevers, a group of acute infections that can cause organ damage, including bleeding and damage to

the liver, kidneys, and other organs, are potentially fatal. Numerous symptoms such as a high fever, headache, muscle aches, nausea, vomiting, diarrhea, exhaustion, and a rash can be brought on by hemorrhagic fevers. These symptoms can range in severity from mild to severe. In severe cases, bleeding can occur from the gums, eyes, ears, nose, and other orifices and can also occur internally, leading to organ failure and death.[7] The severity of the illness can depend on the type of virus causing it, as well as the individual's age, overall health, and prior exposure to the virus. There are many different types of hemorrhagic fevers, each caused by a different virus, including Ebola, Marburg, Lassa, Crimean-Congo, and others. The viruses are primarily transmitted to humans from animals such as rodents, bats, or other mammals, but can also be transmitted from person to person through close contact with the blood or bodily fluids of an infected individual.[8,9]

Endothelial Cells

The inner surface of blood vessels and lymphatic vessels is lined with ECs, forming a seamless barrier. They play important roles in regulating blood flow, and blood pressure (BP) and preventing blood clotting. They also participate in regulating the immune system and play a key role in angiogenesis and the formation of new blood vessels. [10] ECs secrete several signaling molecules that regulate vessel growth and remodeling as part of the angiogenesis process, which involves the formation of new blood vessels. Nitric oxide (NO), endothelins, angiopoiesis-stimulating factor (ASF), interleukins (ILs), tumor necrosis factor (TNF), chemokines, and others are among the molecules.[11] These signaling molecules play an essential role in various physiological processes such as the regulation of BP, the regulation of inflammation, the regulation of angiogenesis, and the regulation of immune responses. In addition, ECs have significant roles in many human diseases such as cancers, hypertension-related diseases, strokes, and cardiac diseases.[3] Hence, they have become topics of interest in the development of such diseases, including viral infections.

Role of Endothelial Cells in Hemorrhagic Fevers

Hemorrhagic fevers brought on by different pathogens often involve ECs, which line the inside of blood vessels. In response to pathogen invasion, EC integrity may be compromised, leading to symptoms such as vasculitis, increased blood vessel permeability, and decreased coagulation,[12] resulting in the hallmark symptoms of hemorrhagic fevers, including bleeding and hemorrhages. In addition to the direct harm brought on by pathogens, EC disruption can also be a result of the host's immune response. Hemorrhage may occur as a result of the blood-vessel barrier dissolving due to inflammatory cytokines, oxidative stress (OS), or immune cell-mediated damage.[13,14]

ECs have specific forms related to tissues and vascular beds, and this variability of these cells plays an important role during different viral infections by regulating the extent of their acceptability and susceptibility to these infections.[15] Hence, understanding the mechanisms by which pathogens and the host immune response contribute to EC damage is critical for developing better treatments for hemorrhagic fevers. Further research into the molecular mechanisms underlying blood-vessel barrier disruption will also aid in the development of new therapeutic approaches to reduce the symptoms and progression of hemorrhagic fevers.[16]

In VHFs, different factors and viral interactions are involved, which play an important role in ECD, and the major ones are depicted in Figure 1.

Endothelial Cell Dysfunction

ECD is a condition in which the cells that line the interior surface of blood vessels do not function properly. This can lead to various health problems such as atherosclerosis, hypertension, thrombosis, inflammation, and the like. Atherosclerosis causes the development of plaques in the arteries, leading to reduced blood flow and an increased risk of a heart attack or a stroke, and elevated BP (i.e., hypertension) may arise accordingly.[17] Again, thrombosis—the formation of blood clots—resulting from ECD may increase the risk of a heart attack or a stroke. Inflammation also occurs in ECD due to the activation of the immune system and the release of cytokines, leading to OS and cellular damage.[11] Endothelial dysfunction is

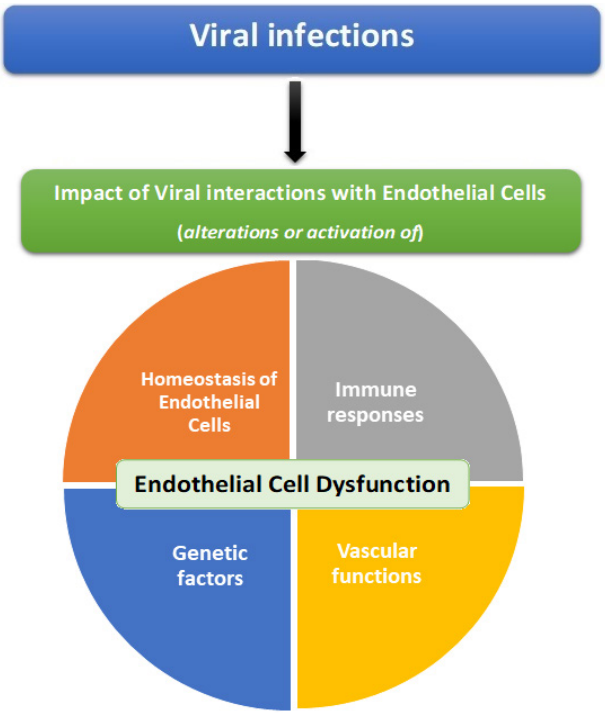

Figure 1. Viral Interactions and Their Impact on Endothelial Cells During Viral Hemorrhagic Infections

frequently associated with aging, smoking, high blood glucose levels, high blood cholesterol levels, high BP, and a sedentary lifestyle.[18]

The endothelium is involved in maintaining homeostasis, vascular function, immune responses, and capillary permeability, and during infections, viruses directly or indirectly interact with EC, leading either alterations or activation of these factors to contribute to the development of ECD.[19]

Mechanisms Involved in the Development of Endothelial Cell Dysfunction

ECD is a multifaceted process influenced by numerous molecular mechanisms. Some of the key molecular mechanisms involved in the development of ECD include inflammation, OS, endothelial NO synthase (eNOS) dysfunction, atheroma formation, vascular smooth muscle cell proliferation, altered expression of adhesion molecules, and the like.[20]

ECs regulate vascular permeability through different signaling processes in a variety of tissues and circulations to prompt proper responses and prevent lethal capillary leakages. The mechanisms behind capillary leakage during viral infections are not fully understood due to difficulty in studying the impact of viral components on endothelium. Some research studies have pointed out that virally induced inflammatory immune responses by the production of chemical mediators such as cytokines (TNFs and ILs) lead to the phenomenon of the 'cytokine storm'. This phenomenon causes the 'acute respiratory distress syndrome' due to 'severe endothelial dysfunction' in influenza infections and recently in a coronavirus-19-like Disease.[21-23]

Usually, chronic inflammation can lead to OS and the activation of pro-inflammatory signaling pathways, which can contribute to the dysfunction of ECs. OS, which results from an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, can lead to damage to ECs and contribute to their dysfunction.[11] eNOS is an enzyme that generates NO, a key signaling molecule in endothelial function. ECD can be caused by eNOS dysfunction, which results in decreased NO production.[20] Again, atheroma, a build-up of fatty deposits within blood vessels, can cause EC damage and contribute to their dysfunction. Smooth muscle cell proliferation within blood vessels can result in the formation of thickened, stiff blood vessels, which can exert a role in ECD.[24,25] Adhesion molecules are essential in the regulation of leukocyte trafficking and the maintenance of vascular homeostasis. ECD can be exacerbated by altered expression of these molecules.[26] These are just a few of the many molecular mechanisms that contribute to the development of ECD. Understanding these mechanisms is crucial for the development of effective treatments for this condition.

Genetic Factors in Endothelial Cell Dysfunction

Genetic factors can play a role in the development of ECD. Some genetic variations have been associated with an increased risk of developing cardiovascular disease (CVD). These include mutations in the *eNOS* gene, the lipoprotein lipase (*LPL*) gene, the angiotensin-converting enzyme (*ACE*) gene, the endothelial adhesion molecule gene, the apolipoprotein E (*APOE*) gene, and the like.[27,28] Mutations in *eNOS* genes can lead to decreased production of NO, which is an important signaling molecule involved in maintaining endothelial function. Again, mutations in the *LPL* gene can increase the levels of triglycerides in the blood, contributing to the development of atherosclerosis and ECD.[18] Variants of the *ACE* gene have been linked to an increased risk of developing CVD, including hypertension and ECD.[6] Variations in genes that regulate adhesion molecules (e.g., the selectin genes) have been linked to an increased risk of CVD and ECD. Variants of the *APOE* gene have been associated with an increased risk of developing CVD and ECD.[29] The Pichinde virus during infection triggers the induction of the *NOS* gene to increase NO production, resulting in enhanced EC permeability to contribute to ECD.[30]

It is important to note that genetic factors are just one aspect of the complex, multifactorial causes of ECD. Other factors such as lifestyle habits, environmental exposures, and health conditions can all contribute to the emergence of this condition.

Role of Endothelial Cells in Angiogenesis

ECs are essential in the process of angiogenesis or the formation of new blood vessels. ECs divide and differentiate during angiogenesis, resulting in the formation of new blood vessels that sprout from the existing vessels. ECs secrete a variety of signaling molecules that regulate this process, including vascular endothelial growth factor (VEGF), FGF, and angiopoietins.[10] ECs also regulate blood vessel permeability, which is critical for the proper functioning of new vessels. They secrete a variety of signaling molecules that attract and activate other angiogenesis-related cells such as pericytes and smooth muscle cells.[31] Viral interactions with the host's ECs lead to the alteration of the angiogenesis mechanisms of ECs, resulting in vascular leakage and inflammatory responses. Recently, in severe acute respiratory syndrome coronavirus 2 infections, researchers have observed increased angiogenesis markers such as VEGF-A. This increased expression of VEGF-A adversely impacts ECs, causing vascular leakage and elevated inflammatory cell responses. This indicates that viral interaction with angiogenic factors such as VEGF results in its overexpression and aids in the virus's pathogenesis mechanism in the host.[32]

In some diseases such as cancer and age-related macular degeneration, the process of angiogenesis is disrupted,

leading to abnormal blood vessel growth. This can cause a range of symptoms and complications such as vision loss, bleeding, and an increased risk of tumor spread. On the other hand, the stimulation of angiogenesis can also be used for therapeutic purposes such as promoting wound healing and tissue repair.[33] ECs play a critical role in the process of angiogenesis, forming new blood vessels from the pre-existing ones. The varieties of participation by ECs in angiogenesis are described below.

ECs divide and migrate at the site of angiogenesis to form new blood vessels. To invade and expand into the surrounding tissue, ECs secrete proteases that break down the extracellular matrix. The new blood vessel's lumen is formed by ECs self-assembling into a tube-like structure. To create the blood vessel's basement membrane, ECs secrete extracellular matrix elements such as collagen and laminin. Growth factors and other signaling molecules that control blood flow through the new blood vessels are released by ECs. ECs regulate the blood vessels' permeability, ensuring that nutrients, oxygen, and waste products are properly exchanged between the blood and tissues.[4,25]

Angiogenesis is a tightly regulated process, and changes in the function of ECs can result in abnormal blood vessel growth and function, leading to various diseases such as cancer, age-related macular degeneration, and CVD. In conclusion, ECs are essential for angiogenesis because they form, maintain, and control the development of new blood vessels.[10,34] For creating novel therapeutic approaches for diseases characterized by abnormal blood vessel growth and function, it is essential to comprehend the role of ECs in angiogenesis.

Regeneration of Endothelial Cells

ECs have the ability to regenerate and heal themselves after suffering harm or injury. To keep the blood vessels functioning properly and fend off various diseases, it is crucial to do this. Proliferation, migration, differentiation, and the recruitment of circulating endothelial progenitor (CEP) cells are some of the mechanisms that contribute to EC regeneration.[35] ECs can divide and multiply to replace damaged cells. This is particularly important in response to injury or disease. ECs can move and migrate to the site of harm or damage and can multiply and create new blood vessels there. ECs have the capacity to mature into functional ECs that can connect with the already-present blood vessels. The blood contains immature cells called CEPs that have the potential to develop into mature ECs. They can be recruited and sent to the injured or damaged area to help with the healing process.[36,37]

Factors Causing Damage to the Endothelial Cells

EC damage can result from a number of factors, which can also cause endothelial dysfunction and other health issues.[38] They can be classified into intrinsic and extrinsic factors.

Intrinsic Factors

Several physiological issues cause damage to ECs and can be coined as "intrinsic factors". The build-up of plaques in the arteries, due to atherosclerosis, causes the blood vessels to become congested, which leads to reduced blood flow and an increased risk of a heart attack or stroke. High BP can cause damage to ECs and increase the risk of CVD. OS and EC damage brought on by high blood glucose levels can increase the risk of diabetes and CVD. Elevated blood cholesterol levels can contribute to the formation of plaques in the arteries, leading to reduced blood flow and an increased risk of a heart attack or a stroke. ECs may become damaged due to OS brought on by immune system activation and the release of cytokines, resulting in inflammation.[11,38] Finally, aging is associated with decreased EC function and an increased risk of CVD and other health problems.

Extrinsic Factors

Some external interferences also play major roles in causing damage to the EC known as extrinsic factors. Certain infections such as HIV and hepatitis C can cause damage to ECs and increase the risk of CVD and other health-related problems. Exposure to numerous environmental pollutants such as heavy metals and air pollution can harm endothelium cells and produce OS, raising the risk of CVD and other health issues. Smoking can increase the risk of cancer and CVD by causing OS and EC damage. The function of ECs can be hampered by inactivity, increasing the risk of CVD and other problems related to health.[11]

Pathogen-Mediated Damage

Pathogens can harm ECs in a variety of ways. Numerous pathogens, including bacteria and viruses, elicit the immune system's response and trigger the release of cytokines, which can harm ECs and lead to OS.[39] Some pathogens such as viruses can infect ECs directly and cause damage. For example, HIV can affect ECs and cause infection, leading to some health problems, including CVD and a decline in cognitive function. Some pathogens, including bacteria and viruses, can cause thrombosis or the development of clots inside blood vessels. This can reduce blood flow and cause damage to ECs, increasing the risk of a heart attack or a stroke. An immune response to a pathogen may result in OS in ECs, particularly if this response is excessive or out of control. Co-infection with different pathogens can exacerbate damage to ECs, which may lead to more severe health problems.[40] In Dengue infections, vascular leakage associated with ECD is an indicator of the severity of this disease. Viruses can directly infect ECs, triggering the production of many inflammatory mediators to cause ECD. Type I interferons play a significant role in modulating and enhancing the TNF-α-mediated angiogenesis process, leading to ECD

and vascular leakage and causing hemorrhagic fevers in patients.[41] Furthermore, during dengue infection, the interaction of the dengue virus with its host triggers an autoimmune response where viral non-structure protein I antibodies cross-react to induce caspase-dependent EC apoptosis through NO production, leading to the dysfunction of ECs.[42] Hantavirus infections cause renal failures in humans, and during its pathogenesis mechanisms, the virus is capable of causing infection without any cytopathic effect in its host. Some researchers have proposed the possible role of viral interaction with the host's neutrophils and neutrophil-associated factors to increase vascular permeability and in turn, aiding the virus's immunopathogenesis mechanism.[43,44] It is crucial to identify and treat pathogen-induced EC damage because it can lead to many diseases such as CVD, infections, and other chronic conditions. Antibiotics, antivirals, or other medications to treat the underlying infection may be used as treatment options in addition to lifestyle changes to support the health of ECs.[45]

Pathogen-induced Hemorrhagic Fever

Viruses, bacteria, and parasites are examples of pathogens that can cause pathogen-induced hemorrhagic fever.[10] The illnesses are characterized by a high fever, substantial bleeding, and EC damage, which may also cause a blood vessel fluid leak among other symptoms. A high fever, bleeding, and blood vessel damage, for instance, are the characteristics of the Ebola virus disease. The symptoms of Marburg virus disease include a high fever, bleeding, and blood vessel damage.[16] High fever, jaundice, and blood vessel damage are all symptoms of yellow fever.[16,46] High fever, bleeding, and blood vessel damage are all symptoms of dengue fever.[47] The Lassa virus is to blame for Lassa fever, which is characterized by a high fever, bleeding, and blood vessel damage.[1] The Rift Valley fever virus is the cause of this illness, which is characterized by a high fever, bleeding, and blood vessel damage.[48]

Outcomes of Pathogen-Induced Hemorrhagic Fever

The results of pathogen-induced hemorrhagic fevers may differ depending on the type of pathogen and the intensity of the infection. Viral infections can disrupt the vascular function of ECs via the host's defense mechanisms. However, some scenarios are generally possible. The mortality rate of hemorrhagic fevers can range from a few percent to over 50% depending on the type. Although healing from the illness may take a few weeks or months for some patients, some may endure long-term repercussions such as fatigue, weakness, and other symptoms. For some patients, long-term health problems may include symptoms such as joint pain, hearing loss, kidney problems, or other conditions. Neurological side effects such as confusion, seizures, or other symptoms are possible in certain patients.[47] The disease can occasionally be transmitted from person to person, which could cause epidemics. If someone encounters the signs of hemorrhagic fever, they must consult a doctor right away since timely care can improve results while reducing the risk of major health problems.

Influence on the Endothelial Cells

Hemorrhagic fevers caused by viruses or other infections can have a serious negative impact on ECs.[49] The pathogen may have several effects, including OS, EC destruction, fluid leakage from blood vessels, and other symptoms. An immunological reaction and inflammation brought on by the virus may worsen the already existing damage of ECs. The pathogen can lead to thrombosis, which is the development of clots inside blood vessels, which can restrict blood flow and harm ECs.[17] Coagulation failure brought on by the illness might raise the risk of bleeding and other symptoms.

These effects may exacerbate a variety of medical conditions such as fluid loss, organ failure, and even death. If someone notices the symptoms of hemorrhagic fever, they should visit a doctor right away because prompt treatment can improve outcomes while lowering the chance of serious health issues. Fluid replacement therapy, supportive care, and antiviral or antibiotic therapy are all options for treating the signs and symptoms of fluid loss and bleeding.[50]

Consequences of Endothelial Cell Dysfunction

ECD can have significant consequences for overall health and well-being. Some of the more specific consequences are as follows:

1. Atherosclerosis: ECD can contribute to the development of atherosclerosis, which is the build-up of plaques in the arteries. Plaques can narrow the arteries and reduce blood flow, increasing the risk of heart attack and stroke.
2. Hypertension: ECD can lead to high BP, which can increase the risk of heart attack, stroke, and kidney damage.
3. Chronic inflammation: ECD can cause chronic inflammation, which can contribute to the development of various health problems, including heart disease, stroke, and cancer.
4. Thrombosis: ECD can lead to the formation of blood clots within the blood vessels, which can cause blockages and reduce blood flow, leading to serious health problems such as heart attack and stroke.
5. Impaired wound healing: ECD can cause wounds to heal slowly and with a higher risk of infection.
6. Decreased immune function: ECD can weaken the immune system, making it more difficult to fight off infections and other diseases.
7. Cognitive decline: ECD can contribute to the development of cognitive decline and memory

problems in older adults.

These are just a few examples of the many consequences of ECD.[3,5,25,51]

Prevention of Damage to the Endothelial Cell

EC damage can be avoided by altering one's lifestyle and partaking in actions that advance cardiovascular health. Eating a healthy diet that is low in saturated fat, trans fat, and cholesterol and high in fruits, vegetables, whole grains, and lean protein can help prevent EC damage and promote cardiovascular health. Obesity and overweight people are more likely to develop CVD and EC damage. Maintaining a healthy weight through diet and physical activity can help prevent this damage.[52] Regular physical activity can enhance cardiovascular health and prevent EC damage. Related examples include brisk walking, jogging, cycling, and swimming. Smoking significantly increases the risk of CVD and EC damage. Giving up smoking can lessen the risk of developing serious health issues and help stop this damage.[53,54] Chronic stress can increase the risk of EC damage and CVD. Finding healthy ways to manage stress, including through exercise, mindfulness, or therapy, can help prevent this damage.[45,55,56] High blood sugar levels can raise the risk of diabetes and CVD and cause damage to ECs. This harm can be avoided by keeping an eye on blood sugar levels and controlling them through food, exercise, and medication, if necessary. High BP and high cholesterol levels are significant risk factors for EC degeneration and CVD. Regular monitoring and appropriate treatment can help prevent this damage.[57-59]

These are just a few examples of the many steps that can be taken to prevent damage to ECs. To find the most effective methods for preserving cardiovascular health and avoiding EC damage, it is crucial to consult a healthcare expert.

Treatment

Even though the prevention of ECD typically involves lifestyle changes such as exercise, diet, and quitting smoking, as well as medications to control BP, cholesterol levels, and blood glucose levels, in some severe cases, surgery or angioplasty may be necessary to restore normal blood flow.[57-59] Pathogen-induced hemorrhagic fevers may be treated with antiviral or antibiotic therapy, supportive care, and fluid replacement therapy to treat the signs and symptoms of fluid loss and bleeding.[50] It is equally important to stop the spread of these illnesses because they have the potential to be extremely contagious and cause outbreaks. The underlying cause of ECD will determine the best course of treatment.[60] However, medications, surgery, EC transplantation, stem cell therapy, and lifestyle modification are some general approaches that may be used, which are explained as follows:

1. Medications: Depending on the cause of ECD, medications such as antiplatelet drugs, cholesterol-lowering drugs, BP-lowering drugs, or anti-inflammatory drugs may be prescribed to improve endothelial function and reduce the risk of serious health problems.
2. Surgery: In some cases, surgery may be necessary to treat underlying conditions that contribute to ECD, including blockages in the blood vessels.
3. EC Transplantation: In some cases, the transplantation of healthy EC may be performed to improve endothelial function and reduce the risk of serious health problems.
4. Stem Cell Therapy: Stem cell therapy may be used to regenerate damaged or diseased ECs and improve overall cardiovascular health.
5. Lifestyle Modification: Making changes to lifestyle habits, such as reducing stress, eating a healthy diet, engaging in regular physical activity, and quitting smoking, can improve the function of ECs.

These are just a few examples of the many treatment options that may be used to treat ECD.[45,57-59] The most appropriate treatment will depend on the underlying cause of the dysfunction, as well as the individual patient's overall health and medical history. It is important to work closely with a healthcare professional to determine the best treatment plan for your specific needs.

Conclusion

Finally, ECD is important in the pathogenesis of hemorrhagic fevers. The development of novel therapies and treatments for these diseases depends critically on our understanding of the mechanisms underlying this dysfunction. Over the past few years, significant progress has been made in our understanding of the mechanisms of ECD in hemorrhagic fevers. We still need extensive learning about this intricate process, and more study is required to improve our comprehension of how ECD contributes to these illnesses.

In conclusion, this review emphasizes the significance of comprehending how hemorrhagic fevers cause ECD and the potential for creating novel therapies to treat these severe and potentially fatal illnesses. In addition to advancing our knowledge of the pathogenesis of these conditions, further study in this field may also result in the creation of novel, more potent hemorrhagic fever treatments.

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Competing Interests

There is no conflict of interests.

Ethical Approval

Not applicable.

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