

Review Article

A Narrative Review on Argentine Hemorrhagic Fever: Junin Virus (JUNV)

Monira Sultana¹, Nujhat Nabilah², Syed Mahmood Shahidul Islam³, Md Ishtiaque Uddin⁴, Asma Sadiya Nisha⁵, Marzia Feruz Snigdha⁶, Mst Zarin Islam⁷, Nikolaos Syrmos⁸, Sadia Afrin^{9*}, Md Rezwan Ahmed Mahedi¹⁰

¹Department of Pharmacy, Dhaka International University, Bangladesh

²North South University, Department of Public Health, Bangladesh

³Divisional Health and Safety Officer (South Asia and Central Asia); SMEC International Pty Ltd, Bangladesh

⁴International Islamic University Chittagong, Bangladesh

⁵Department of Pharmacy, The University of Asia and Pacific, Bangladesh

⁶Department of Public Health, State University of Bangladesh

⁷Rangpur Medical College, Bangladesh

⁸Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece

⁹Department of Pharmacy, Comilla University, Cumilla, Bangladesh

¹⁰Research Secretary, Bangladesh Pharmacists' Forum (Comilla University), Bangladesh

*Correspondence author: Sadia Afrin, Department of Pharmacy, Comilla University, Cumilla, Bangladesh; Email: sadiayaffa747@gmail.com

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Abstract

Epidemic cases of Argentine hemorrhagic fever (also known as AHF) have been associated with the Junin virus, also known as JUNV, ever since the 1950s. The JUNV arenavirus is endemic to the countries of the New World. In this study, we will attempt to communicate the current level of knowledge on the morphology, transmission, replication and epidemiology of the Junin virus (JUNV). We examined both PubMed and Google Scholar in order to discover the most recent research on the Junin virus. The virus is indigenous to the humid pampas of Argentina, where it is propagated by the aerosolization of host rodent excrement. In recent years, considerable advances have been made as new technologies have increased understanding of how the Junn virus replicates. We will focus on recent studies that aim to understand the attenuation of viruses by examining their biological mechanisms. We will also provide a brief overview of what is currently known about the pathogenesis of the Junn virus, with an emphasis on treatments, morphology, transmission, replication and epidemiology.

Keywords: JUNV; Epidemic; AHF; Calomys Musculus; Viral Replication; Rodents; Hemorrhagic Fever

Introduction

Since the 1950s, the Junin virus, also known as JUNV, has been linked to epidemics of Argentine Hemorrhagic Fever (AHF) [1]. JUNV is an arenavirus that is native to the New World. It is most often passed from people to other humans by the inhalation or consumption of droplets, dust, or food that has been contaminated with urine from rodents. Calomys musculus is considered to be the primary natural host of JUNV; nevertheless, the virus has also been discovered in other species of rodents [2]. It is an enclosed, round, oval, or

pleomorphic virion, measuring approximately 110 nm to 300 nm in diameter (the average is 120 nm) and it possesses a single-stranded bi-segmented RNA genome. This virus is identical to all other arenaviruses [3]. While the exterior of the virion has projections in the shape of hollow golf clubs, the inside of the virion includes granules that are similar to grains of sand and are distinctive of the family Arenaviridae [4]. It enters cells using a process known as clathrin-mediated endocytosis, which is distinct

from the one used by the Old-World arenavirus Lymphocytic Choriomeningitis Virus (LCMV). Immediately after entering the host cell, JUNV is transported to endosomes, which is where the pH-dependent membrane fusion process takes place. The first phases of JUNV infection have been explored, which has offered information on the way by which the virus enters the host [5]. There have been a few reports of an immune plasma therapy and an off-label combinational use of ribavirin and favipiravir. Both of these treatments are considered experimental [6]. A live attenuated vaccine was created by the US Army Medical Research Institute of Infectious Diseases. However, because to concerns over the genetic stability of the vaccine, it has only been licensed for use in regions where the disease is endemic [7].

Objective

This review aims to convey the present state of knowledge on Junin Virus (JUNV) morphology, transmission, replication and epidemiology.

Methodology

To locate the current literature on junin virus, we searched PubMed and Google Scholar. Various combinations of the following MeSH terms: (JUNV) and (Transmission); (JUNIN) and (Replication); (JUNIN) and (Epidemiology); (JUNIN) and (Genome); (JUNIN) and (Morphology); (JUNIN) and (Pathogenicity); (JUNIN) and (Therapeutics); (JUNIN) and (Drugs); (JUNIN) and (Medicine). To narrow the focus, we only looked at journals released between 1961 and 2023. After individually reviewing the pieces, the authors gathered to share their thoughts. The goal of this research technique was to locate published materials that described the evolution, spread and spread of JUNV in the modern world.

Epidemiology

The rich agricultural plain in the center of Argentina that is known as the "humid pampas" is home to a strain of the Junin virus that is only found there [8]. The appearance of AHF in the 1950s has been hypothesized to have been caused by human modifications of the environment in connection with agricultural activities [9]. This would have happened around the time the disease was first discovered. The endemic region encompasses over 150,000 km² and has a population of over 5,000,000 people [10]. It is located to the north of the province of Buenos Aires, southeast of Cordoba, south of Santa Fe and northeast of La Pampa. Since the advent of the AHF, there has never been a lull in the occurrence of yearly outbreaks, which typically range in size from three hundred to one thousand cases. The majority of human infections take place between the months of April and July, which coincides with an increase in agricultural activities that make it easier for people to come into contact with the rodent reservoirs of the Junin virus which also reach their highest population levels during this time period [11]. In point of fact, during this time period 75% of human patients with AHF are male agricultural laborers who are active in the harvesting of crops [12].

Rodents, which are prone to persistent infections caused by JUNV, are migratory within their natural environment. Infection may occur in humans by mucosal exposure, the inhalation of infectious particles in aerosol form, or through direct contact of abraded skin with infectious material. Transmission from one person to another is very uncommon, although it is possible for it to take place via direct contact with the contaminated bodily fluids of a viremic patient. Additionally, nosocomial infections have been documented [13]. In Argentina, major epidemics tend to take place mostly during the harvesting season, with the month of May being the month with the highest incidence rate. The illness strikes men four times more often than it does women and it is more common in those who work in rural areas than it is in people who live in metropolitan areas. There is a positive correlation between the yearly incidence of AHF and the local population densities of the reservoir species, which is the drylands vesper mouse (*Calomys musculinus*) [14]. The vaccination of high-risk people has the effect of further altering the epidemiologic pattern of illness [15].

Genome and Morphology Structure

A viral envelope that is composed of a phospholipid bilayer and glycoproteins surrounds the Junin Virus. Its shape might be spherical or pleomorphic, which means it, can take on a variety of forms. It has a diameter of 110-130 nm and contains multiple glycoprotein spikes that are each 8-10 nm long and are lodged in the lipid bilayer. Important for facilitating attachment to and entrance into host cells is a layer of T-shaped glycoprotein extensions on the surface of the particle, extending outwards for up to 10 nm from the envelope. These spikes are composed of the glycoproteins GP1 and GP2, which are released into the environment when the Glycoprotein Precursor (GPC), a protein that is encoded in the viral genome, is cleaved. The glycoprotein

spike has the form of a club, with the "head" of the club being made up of a GP1 tetramer and the "stem" of the club being made up of a GP2 tetramer. Another protein that is encoded in the viral genome is called the Nucleoprotein (NP) and it works in conjunction with viral RNA to produce nucleocapsid structures in the cytoplasm of infected cells. The lipid membrane of the virus has its beginnings in the membrane of the host cell and ribosomes, which also originate from the host cell, are packed inside of it. It is not known at this time whether or not the ribosomes serve any role [16].

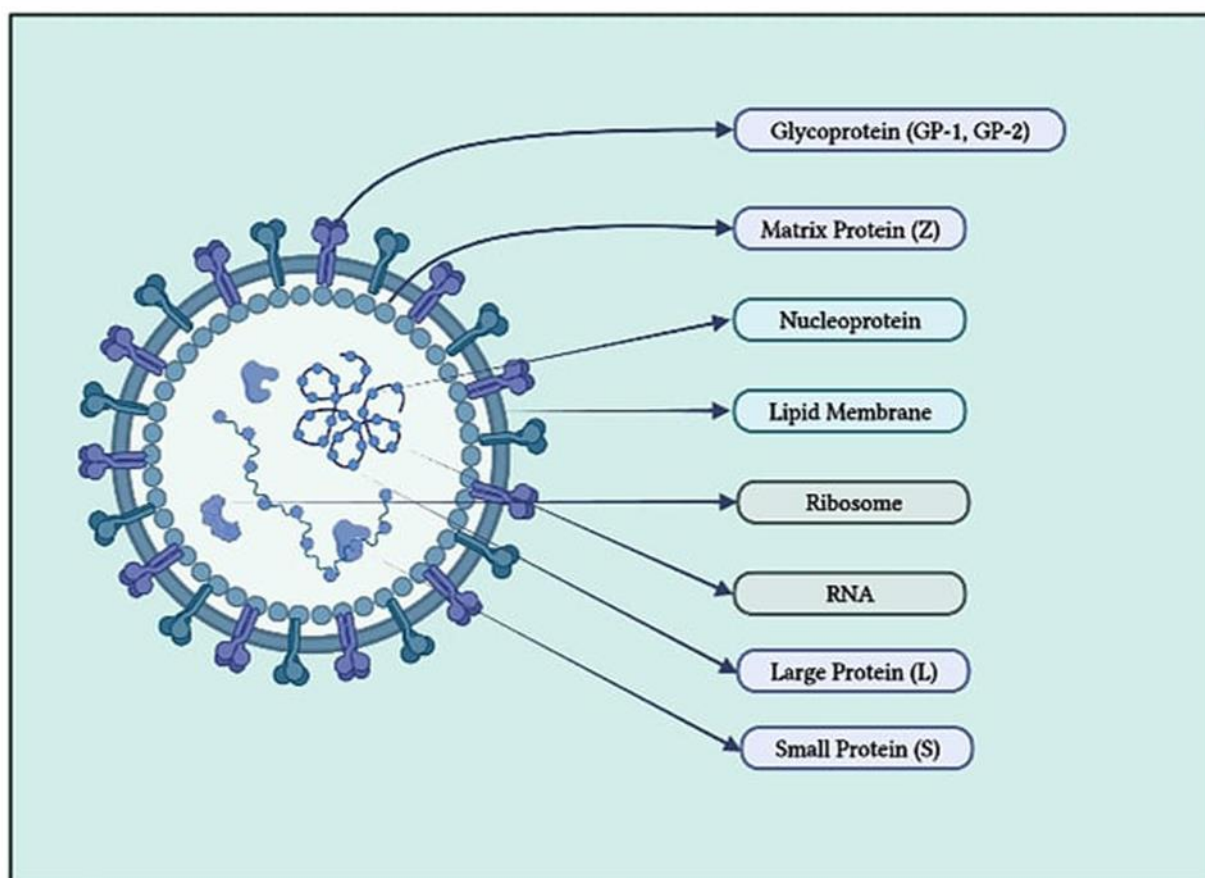


Figure 1: Morphological structure of Junin Virus (JUNV).

The genome of the Junin virus consists of two RNA molecules, each of which encodes two genes in an ambisense orientation. As their names suggest, "short" (S) and "long" (L) describe the lengths of the two parts. About 3400 nucleotides long, this fragment codes for both the nucleocapsid protein and the Glycoprotein Precursor (GPC). The T-shaped glycoprotein spike protrudes from the viral envelope and is composed of two viral glycoproteins, GP1 and GP2 [17]. The viral polymerase and a zinc binding protein are both encoded in the lengthy section (about 7200 nucleotides in length). The space between the nucleocapsid and the viral envelope is filled by matrix proteins. They help keep the virus particle together and functioning properly.

Transmission

Calomys musculinus has been shown to be the primary reservoir for the rodent-borne Junin virus. Most human infections occur during agricultural activities during harvest season due to direct contact with or inhalation of aerosolized rat bodily fluids or excreta. Conditions conducive to the unrestrained spread of *Calomys musculinus* are thought to have led to the appearance of AHF in Argentina in the 1950s. The Junin virus is excreted by infected rats in their faeces, urine and saliva. Houses, farms and even food storage facilities are all at risk of contamination from the virus [18]. It is possible for humans to get Junin virus by environmental contact. Contact with rat faeces, breathing in aerosolized virus particles, ingesting tainted food or drink, or having weakened skin or mucous membranes all increase the risk of infection. Farmers, field workers and others who manage rodent populations in rural areas are more likely to be exposed to Junin virus because of their occupations. Although human-to-human transmission is rare, severely viraemic individuals may cause nosocomial epidemics in healthcare settings [19]. The average

incubation period is 7 days, although it may be as long as 21 days in certain circumstances. Since then, hundreds of cases have been recorded annually, however the occurrence of AHF has greatly reduced because to the availability of the very successful live-attenuated Candid#1 vaccine beginning in the 1990s [20].

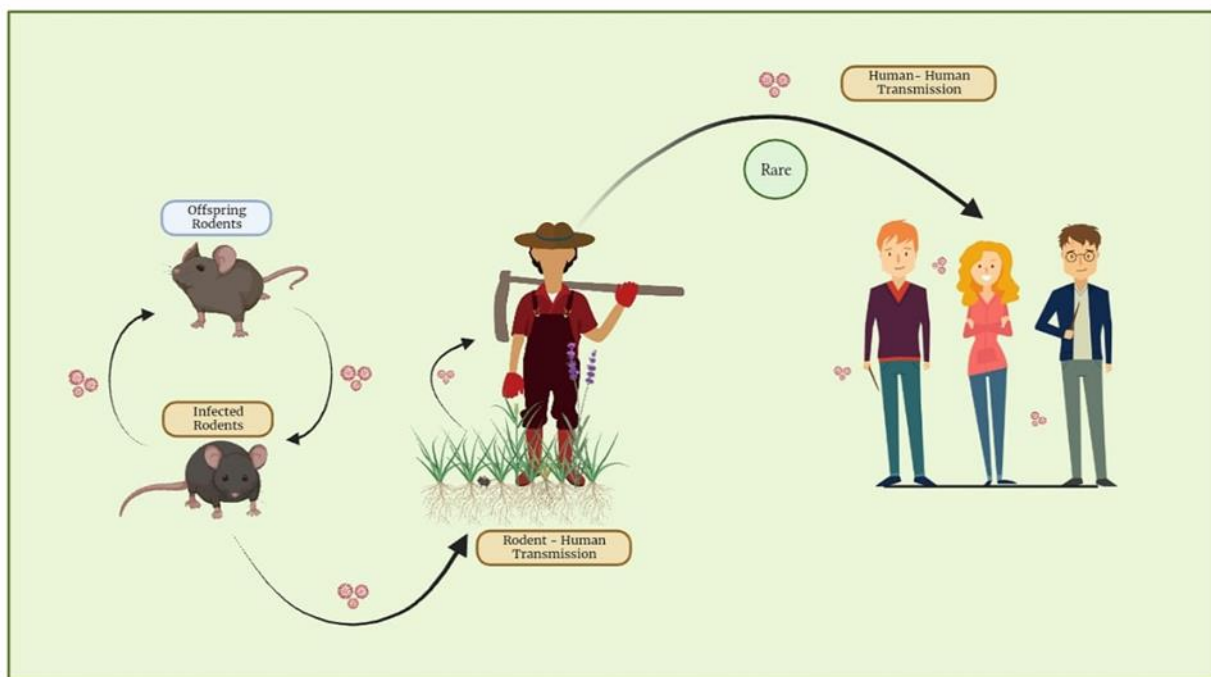


Figure 2: Transmission of JUNV through infected rodents to human. Basically, the persons are directly connected to agricultural works, prominent to this infection. Human-human transmission can be possible but rare in cases.

Replication

The Junin virus will first attach itself to a particular receptor on the surface of the host cells known as human transferrin receptor 1 (hTfR1) [21]. There is still a lack of complete understanding about the particular receptors that the Junin virus uses in order to gain access. After it has attached itself to the host cell, the virus enters the cell by a process called clathrin-mediated endocytosis, at which point it is absorbed by the membrane of the host cell and imprisoned inside an endosome. A conformational shift in the viral glycoproteins is triggered inside the endosome as a result of the low pH environment. This change makes it possible for the viral envelope to fuse with the endosomal membrane. During this stage of the fusion process, the viral nucleocapsid is released into the cytoplasm of the host cell [22]. The presence of acidic conditions in the endosome is necessary for the fusion process to take place. When the pH of the endosome is lower than 6.1, the virus is able to combine with the membrane of the vesicle. The need of a low pH level is not completely explained by the available evidence. After the Junin Virus has successfully entered the cell by clathrin-mediated endocytosis, the PI3K/Akt signalling pathway is initiated, which transports the virus to a more acidic compartment of the endosome. The viral nucleocapsid, which is composed of the viral RNA genome and the nucleocapsid proteins that are firmly connected with one another, is released into the cytoplasm [23]. The L segment of the viral genome is responsible for encoding an enzyme known as viral RNA-dependent RNA polymerase (RdRp), which is responsible for starting the replication process. The RdRp is responsible for the synthesis of complementary positive-sense RNA strands from the negative-sense genomic RNA. These strands then function as replication templates for subsequent processes. The RdRp complex is responsible for performing the transcription step, which results in the production of a collection of subgenomic RNAs (sgRNAs). These sgRNAs hold the coding information for viral proteins, including as glycoproteins, matrix proteins and other non-structural proteins. Viruses use this information to construct their own proteins. The ribosomes of the host cell are responsible for translating the sgRNAs, which results in the production of viral proteins that are necessary for viral assembly and replication. Within the host cell, the newly synthesised components of the virus, such as viral RNA and viral proteins, come together. Both the process of budding and the assembly of the viral nucleocapsid are coordinated by the viral matrix proteins, which play a role in both processes. The mature viral particles emerge from the host cell, at which point they acquire an envelope

that is produced from the membrane of the host cell. The freshly generated Junin virus particles are expelled from the infected host cell in one of two ways: either the cell is lysed, or budding occurs from the surface of the cell. The replication cycle may then continue since these virus particles can infect other cells and spread the infection [23].

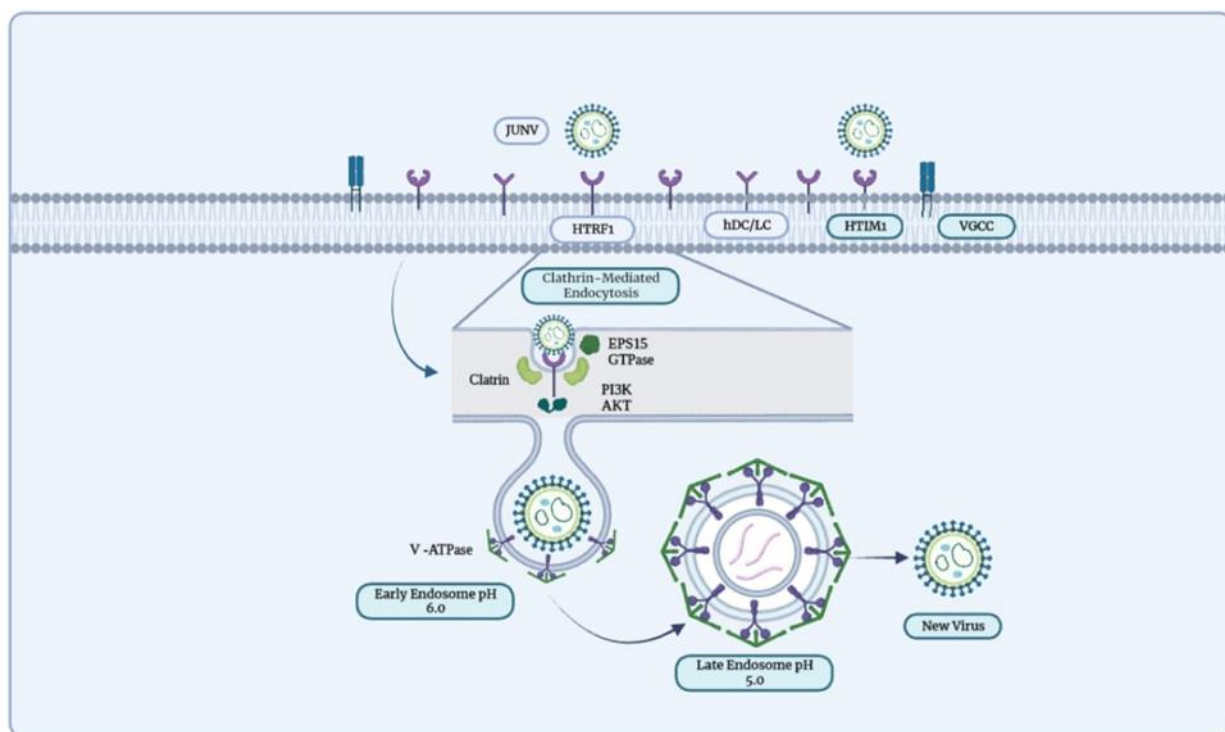


Figure 3: Schematic representation of JUNV life cycle. For details, please see text. Infection with the JUNV virus. For entry into cells, JUNV primarily employs hTrf1. There are three types of receptors that JUNV employs that are not part of the canon: (i) the hTIM-1 phosphatidylserine receptor; (ii) lectin receptors like hDC-SIGN and hL-SIGN; and (iii) voltage-gated calcium channels (VGCCs). The PI3K/Akt signaling pathway is then rapidly triggered once JUNV is internalized through a clathrin-mediated endocytic route. Then, JUNV moves from Rab5-early (pH = 6.2-6.5) to Rab7-late (pH = 5.0-6.0) endosomes through the cellular endocytic route [20].

Pathogenicity

Eighty percent of those who are infected with Junin virus will develop clinical symptoms. The Argentine Hemorrhagic Fever (AHF), which is caused by the Junin virus, may be divided into three distinct phases: the prodromal, the neurological-haemorrhagic and the convalescence phase [4].

Prodromal phase: In most cases, it will pass one week after the first signs of illness. Chills, lethargy, anorexia, headache, lower back pain and mild fever (38 to 39°Celsius) are only few of the early signs. In addition to these, many people experience retro-orbital discomfort, nausea, vomiting, epigastric pain, photophobia, dizziness, constipation, or mild diarrhea. On examination, the face, neck and upper chest may be red and conjunctival congestion and periorbital edema may be present [4]. Gums may seem puffy and bleed easily, either on their own or in response to gentle pressure. At this stage, the patient may feel irritated, sluggish and have a little tremor of the hands and tongue. Menstrual bleeding that occurs at other times than the menstrual cycle is a typical occurrence in women [24].

Neurological-haemorrhagic phase: The development of neurological and/or hemorrhagic symptoms typically occurs 8-12 days after the beginning of other symptoms in around 20-30% of instances with AHF. Patients will show signs of shock, bacterial infections and severe hemorrhagic or neurologic symptoms [4]. To name just a few, hemorrhagic symptoms might manifest as blood in the vomit or faeces, blood in the lungs, nasal bleeds, haematomas, abnormal vaginal bleeding, or blood in the urine. The progression from mental bewilderment, pronounced ataxia, heightened irritability and tremors to delirium, generalised

convulsions and coma is a hallmark of the neurological symptoms. It's possible that secondary bacterial infections like pneumonia and septicemia would further worsen the condition during this time [25].

Convalescence phase: Those who make it through the ordeal report a considerable period of recovery, perhaps from a few weeks to a few months. In most cases, the effects of fatigue, irritation, memory loss and hair loss on patients are temporary [9]. Serum from patients who have recovered from AHF (convalescent serum/plasma) can reduce the case fatality of AHF from 10 to 30 percent to 1 percent, but it can also cause a transient neurological syndrome characterized by headaches and tremors in 10 percent of patients who receive convalescent serum.

Therapeutics

At this time, there is no particular antiviral medicine that has been given the green light for use in the treatment of an infection caused by the Junin virus or Argentine Hemorrhagic Fever (AHF). Patients diagnosed with AHF, on the other hand, absolutely need supportive treatment in addition to symptom management. Patients diagnosed with AHF need careful monitoring and treatment that is supportive in order to effectively manage their symptoms and avoid consequences. This may involve the restoration of fluids and electrolytes, the management of organ failure, the treatment of subsequent infections and correction of coagulation abnormalities.

In the laboratory, ribavirin and favipiravir, both of which are considered to be broad-spectrum antiviral medicines, have shown some action against the Junin virus and they have also been employed in clinical settings [26,27]. In certain instances, beginning therapy with ribavirin sooner rather than later has been linked to better clinical results. However, its efficacy in treating AHF is still up for debate and further study is required to identify the most appropriate use of the drug and how well it works [28].

Convalescent plasma therapy has been considered as a treatment option for Argentine hemorrhagic fever caused by JUNV. Convalescent plasma is the only approved treatment for this disease [29]. It has also been used as a treatment option for other viral infections, including Ebola virus and SARS-CoV-2. Also, after immunizing mice with DNA and then screening for antibodies against Glycoprotein Complex (GPC), a series of monoclonal Antibodies (mAbs) was identified. In the end, five mAbs were identified as being very efficient in neutralizing JUNV. Their ability to bind conformational GPC and Glycoprotein 1 (GP1), the latter of which is important for receptor recognition, was further investigated [30-37].

Conclusion

Viral replication mechanism, host-virus interactions, therapy and immunization are all hot topics in the study of Junin Virus. Evidence suggests that the Z protein of the Junin virus may be used to hijack human ribosomal proteins, Ras proteins, endosome sorting proteins and ATP production proteins when infecting a human host. Using the human Type 1 Interferon to enter cells is another human protein that the Junin virus has been shown to bind with and hijack. This contact is one mechanism by which the Junin virus may trigger Argentine Hemorrhagic Fever (AHF) after it has entered a cell. The severity of AHF symptoms in mice infected with the Junin virus was observed to correlate with the quantity of Type 1 Interferon in the mice's blood. Studying these factors provides researchers with a more complete picture of JUNV's effects on the host, which in turn may be utilized to make better treatment and immunization options. Antibodies against the Junin Virus are also the subject of investigation and research. The Junin Virus vaccine contains a glycoprotein that has shown promise in defending against other New World arenaviruses, including Machupo. Mice specifically were protected against mortality and infection by the Machupo virus when given a recombinant glycoprotein derived from the Junin Virus strain. These results open the door to the potential of using vaccinations against many viruses. In addition to making life safer for Argentines, ongoing research on better vaccines for the Junin Virus adds to the body of knowledge on how vaccines may be created for other viruses.

Conflict of Interest

The authors have no conflict of interest to declare.

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