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Impact of Human Immunological Responses and Viral Genetic Diversity on Outbreak of Human Monkeypox Virus. A Comprehensive Literature Review Study

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ABSTRACT

Monkeypox was caused by Monkeypox Virus (MPXV) and can infect both humans and animals. An understanding of the interplay between host immunity and genetic diversity was necessary to understand the etiology and epidemiology of monkeypox disease. **Objective:** To clarify how genetic differences and host immune responses interact when a moneypox infection occurs. Furthermore, we also aim to provide insights into individual variability in illness outcomes and possible treatment targets by investigating how distinct genetic profiles affect immune system activation and efficacy. **Methods:** Recent research on monkeypox, concentrating on the immune response mechanisms of the host and genetic variables linked to virus vulnerability have thoroughly analyzed. For this purpose, the data were searched from various research engines such as google scholar, pubmed, medline etc., by using different key words i.e., monkeypox and host immunity, monkeypox and antibodies interactions, monkeypox outbreak, mnkeypox strains. **Conclusions:** The way a monkeypox infection progresses and turns out was greatly influenced by the interplay between host genetic differences and immunological responses. Public health initiatives and the creation of tailored treatment plans can both benefit from the identification of genetic markers linked to immunological response profiles and vulnerability.

INTRODUCTION

The causative agent of monkeypox is the Monkeypox Virus (MPXV), an orthopoxvirus being a part of the Poxviridae family of viruses [1]. The disease is referred to as "monkeypox" as MPXV was first discovered in 1958 in lab monkeys imported from Singapore [2]. It is more likely that rats and other tiny animals serve as the MPXV's natural hosts, nevertheless. Smallpox symptoms are similar to those of human monkeypox, but the former is less deadly [3]. In the 1970s, the MPXV virus was first found in humans in isolated cases throughout several African countries; however, during the next 20 years, the virus spread more broadly throughout Africa [4]. Two possible explanations of the present outbreak are the discontinuation of the smallpox vaccination program and waning immunity to

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smallpox in the general population [5]. Research has demonstrated that vaccination against smallpox confers immunity against monkeypox. During a nationwide smallpox vaccination effort that started 12 years before the commencement of data collecting, early research from Zaire in 1988 indicated that those who had gotten the immunization are around 85% less likely to experienced monkeypox than those who had not [6]. It was found in another study that those who had received the smallpox vaccination had decreased rates of long-term MPXV infection sequelae, severe problems and mortality. According to a recent study on 528 illnesses identified during this outbreak, only 9% of those ill had previously had a smallpox vaccination [7]. It's interesting to note that (MSM) have the highest number of infections associated with the recent outbreaks [8]. The virus that causes monkeypox is becoming more widespread in areas where it is not typically found. Monkeypox has unexpectedly and quickly spread too many different countries, which suggests that unreported transmission may have continued. The number of cases that are reported globally is steadily rising. At least twenty non-African nations, including the United Kingdom, Portugal, Spain, and Canada, had reported over 57662 probable or confirmed cases as of September [9]. Host Immunity to Monkeypox Virus: Innate and adaptive immune responses are both involved in host immunity to the monkeypox virus. The first line of defense is provided by the innate immune system, which does this by triggering inflammatory responses and using pattern recognition receptors to identify viral proteins. Controlling the early phases of infection depends on this first reaction. On the other hand, the adaptive immune system offers a more focused and durable defense [10]. It involves the production of antibodies by B cells that target the virus and T cells that are able to identify and eliminate infected cells. The creation of these particular antibodies and memory cells can be stimulated by vaccination, which results in more potent and long-lasting protection against monkeypox[11]. This is why vaccination is essential for improving adaptive immunity. The goal of continuous research into immune responses to monkeypox is to enhance comprehension and create more potent vaccinations and therapies[12]. Outbreak of Human Monkeypox Virus: The first confirmed case of the Human Monkeypox Virus (hMPXV) in the United Kingdom was reported on May 7, 2022, which heightened concerns about infectious diseases following the COVID-19 pandemic. On July 23, 2022, the World Health Organization (WHO) deemed the monkeypox epidemic a global public health emergency. Clade I denotes the Central African or Congo Basin clade, and clade II will henceforth be used to refer to the West African clade. The World Health Organization is thinking of changing the virus's name to prevent stigmatization. The risk of having recently contracted the monkeypox virus was higher in men (including those who are transgender [13]. The origin of the outbreak is unknown. What led to its spread? The current outbreak is becoming more severe, so we must pay close attention to the rate of person-to-person transmission. We'll be able to tell whether the virus has changed and whether the circulating strain will spread more easily or not. The monkeypox virus cannot be transmitted sexually, however, samples from the vagina or sperm may provide fresh insights on the virus's mechanisms of transmission. Appropriate viral strains, like the Ebola and monkeypox viruses, can proliferate due to alterations in forest settings. Genetic Diversity among Poxviruses: It remains an arduous scientific task to ascertain whether the genetic alterations in the monkeypox virus are the source of the most recent epidemics[14]. For example, compared to the MPXV strains prevalent before 2017, the strain circulating in the 2022 pandemic may have had more DNA insertions and deletions, which could have contributed to the present outbreak [15]. D209N, P722S, and M1741I are three nonsynonymous single nucleotide polymorphisms in surface glycoprotein B21R, a critical target for antibodies, which may increase the virus's transmissibility [16]. The Variola Virus (VARV) exclusively infects humans, in contrast to other growing zoonotic diseases caused by poxviruses that afflict a number of animal species, including cattle, rats, monkeys, and others. The most prevalent clinical symptom of the poxvirus is skin lesions [17]. Two key traits of poxviruses are their genetic diversity and host range [18]. The E3L-encoded protein inhibits both 2′-5′ oligo adenylate synthase and Protein Kinase R (PKR) [19, 20]. Monkeypox Virus (MPXV) strains exhibit genetic heterogeneity, with the majority of these strains falling into the West African and Congo Basin clades. The Congo Basin clade is typically linked to more severe sickness, indicating that these genetic changes impact the virus's pathogenicity. Differences in the genetic makeup of the virus influence its transmissibility, clinical consequences, and ability to elude the host immune response [21]. Since it aids in comprehending the behaviour of the virus and modifying interventions to address changing risks, monitoring these genetic variants is crucial for the development of effective vaccines and public health policies [22]. In a Chinese hamster ovary cell line, VACV replication was restricted after the poxvirus ANK protein was eliminated. CP77, also known as CHOhr, is a protein that has been proven to be a host range factor [23-28]. It is possible that other ANK proteins perform comparable roles, but further investigation is required to confirm this. The genes E3L, C7L, and m62r (part of the C7L family) contain the most diversity of poxvirus homologs. It is anticipated that poxviruses with distant relatives will have

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distinct genes necessary for their host range [29, 30]. Immunity Responses: Neutralizing Antibodies (NAbs) are the primary immunological mechanism via which cross-protection against VACV immunization is mediated [31]. Because of the large variation in strength sand the lack of understanding regarding the molecular pathways governing protection, the degree of efficacy is unknown. Following VACV inoculation via percutaneous injection, a wide range of serum antibody responses directed against different VACV antigenic determinants are triggered. The fact that the sera of immune persons show cross-neutralizing activity against MPXV, VARV, and VACV suggests that these individuals' sera contain different specificities of Abs [32-34]. Although, every orthopoxvirus exhibited a distinct pattern of recognition, it was found that they all shared neutralizing components through polyclonal antibody testing on rabbit immune serum [35]. A significant factor in disease prevention is the smallpox vaccine's induction of strong humoral reactions [36]. Methods to Detect Cross Reactive Antibodies: Antibodies that recognized various related antigens can be identified by using several critical methods for the detection of cross-reactive antibodies. A popular method for testing for antibodies against distinct but structurally similar antigens is the Enzyme-Linked Immunosorbent Assay (ELISA), which can be adjusted [37, 38]. A further technique is Western blotting, which uses size-based protein separation to identify cross-reactive antibodies by their unique binding patterns. Furthermore, assays for neutralization can evaluate an antibody's ability to suppress the activity of different viral strains. In order to create broad-spectrum vaccinations and comprehend immune responses to various infections, these methods are essential [39, 40]. Imunity Mediated Protection Against Monkeypox Infection: Research often use interactions between VACV and multiple orthopoxviruses to examine monkeypox immunity. Research [41-43] suggests that monocytes are the primary target of the poxviruses. The poxvirus antigen found in neutrophils and monocytes is thought to be one of the primary reasons of MPXV mortality [44]. The innate immune system of the body depends heavily on natural killer cells known as monocytes, which also have the power to modify the functioning of the adaptive immune response. The blood and lymph nodes of rhesus macaques infected with MPXV show a substantial increase in natural killer cell numbers [45, 46]. There exists a correlation between the intensity of infection and cytokine responses in animals infected with VARV. MPXV did not substantially activate genes controlled by NF-B and TNF even in infected mice. This makes sense because orthopoxviruses such as VARV contain genes that alter the TNF and NF-kB pathways [47, 48]. Innate Immune Response and Monkeypox Virus Invading: Despite long-standing knowledge of the virus, human immunity to MPXV infection remains unknown. Therefore, to determine the methods by which MPXV interacts with the host immune system, research employing orthopoxviruses identical to VACV are frequently used [49]. The ensuing sections address the potential defense mechanisms of the host against MPXV, in addition to the immunological evasion tactics the virus use during active infection. While certain viruses also target innate immune cells, these cells normally react to an active viral infection first. Poxviruses first target monocytes, according to a number of in vitro and in vivo investigations [50]. Susceptible monocytes are attached to the infection sites when cynomolgus macaques get MPXV infection, with the lungs revealing a large increase in CD14+ monocytes [51]. Additionally, it has been demonstrated that inflammatory murine monocytes that are CD45+CD11b+GR-1int allow VACV multiplication and may even carry the virus. Moreover, human primary M2-like macrophages are claimed to have enabled VACV proliferation and dispersion [52]. One study that revealed a correlation between low blood neutrophil counts and moribundity in animals infected with MPXV indirectly supported our results [53, 54]. Natural killer cells, like monocytes, are essential for innate immunity because they have the ability to steer the trajectory of the adaptive immune response [55]. IgM and IgG Responses: A vital part of the immune system's response to infections are the Immunoglobulin M (IgM) and Immunoglobulin G (IgG) responses and measuring these reactions is essential for understanding and diagnosing a wide range of illnesses [56-57]. When a new infection arises, IgM is usually the first antibody to be generated and is a sign of recent or acute exposure to a pathogen [58-59]. IL-15 can be triggered via type 1 IFN-independent mechanism by IL-15 complex treatment, and this treatment is enough to drive IFN-c expression and lymphocyte responses [60]. Natural killer cell depletion had no effect on virus titers in the early stages of acute LCMV infection or during persistent LCMV infection [61]. Aside from lateral flow testing in fast diagnostic settings, it can be found in the blood by assays like ELISA, which use particular antigens to capture IgM antibodies. IgG, on the other hand, supplies long-term immunity and signifies prior exposure to an infection that has been more thoroughly treated [62, 63]. It also manifests later and stays longer in the bloodstream. It is assessed with methods similar to those for measuring IgM, but frequently with a focus on determining the pathogen's chronicity or history of exposure[64-66]. Immunological status evaluation, treatment and vaccination techniques, and the identification of the infection phase all depend on both IgM and IgG responses [67-68]. In circumstances where the immune system is significantly impaired, the body's capacity to build a successful defence against

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opportunistic infections is hindered.A lower CD4+ T cell count puts a person at higher risk of developing a serious illness from MPXV. Because of this, they experience more severe symptoms of monkeypox, including widespread skin lesions, longer sickness, and higher morbidity [69]. B Cell and Antibodies Mediated Immunity: The earliest evidence of the significance of B cells and immunoglobulins against poxviruses came from the live VACV vaccine, which was employed in the successful worldwide immunization campaign to eradicate smallpox [70, 71]. Additionally, it was shown that Vaccinia Immune Globulin (VIG), which is made from vaccine serum, greatly reduced the risk of smallpox among close relatives of affected individuals96. Particular to VACV, B cell responses helped avoid a deadly MPXV infection in rhesus macaques. Moreover, epidemiological research has notably shown that the VACV vaccine provides defense against several poxviruses, such as MPXV [72]. Monoclonal antibodies (mAbs) have demonstrated great potential in the battle against the Monkeypox Virus (MPXV), providing focused therapeutic alternatives that improve the effectiveness of treatment [73, 74]. In order to neutralise the virus and stop it from infecting or multiplying in host cells, these antibodies are designed to attach only to MPXV proteins. Experimental and preclinical research has indicated that specific monoclonal antibodies can considerably lower viral loads and lessen the severity of the illness in those who are afflicted. Its excellent specificity, which reduces off-target effects and increases antiviral activity, is credited with its efficacy. For those who are at high risk or have been exposed, monoclonal antibodies can also quickly produce passive immunity and offer protection [75–78]. Yet, based on the particular mAbs utilised, when they are administered, and the virus strains that are in use, their efficacy may differ [60, 61]. Enhancing treatment regimens and increasing outcomes for people affected with monkeypox should be possible with the ongoing research on monoclonal antibody treatments against MPXV [79-81]. T Cell Mediated Immunity: HIV-1 infection that is not under control has a major negative effect on CD4+ T cell numbers and makes people far more susceptible to opportunistic infections, such as the Monkeypox Virus (MPXV) [82, 83]. Aided in the coordination of the immune response, HIV-1 targets and eliminates CD4+ T cells. These cells gradually diminish as the infection worsens, which reduces the immune system's capacity to combat infections.Considerably lower CD4+ T cell counts, which can occasionally fall below 200 cells/mm^3-a threshold suggestive of progressive immunosuppression and Acquired Immunodeficiency Syndrome (AIDS) are frequently observed in studies of HIV-1 positive people with poorly managed viral loads [83]. This is because their immune system is compromised and cannot effectively control the virus. It is important to manage HIV-1 efficiently to lower the risk of opportunistic infections, as demonstrated by the interaction between HIV-1-induced immunosuppression and MPXV infection. Compromised immune defences can aggravate the severity and consequences of viral diseases [84-87]. Monkeypox Strains, Their Virulence and Transmissibility: There are two subclades of the monkeypox virus: the Congo Basin and West African subclades. The severity of strains from the Congo Basin and West Africa varies with respect to human and monkey disease, with the former being more virulent in non-human primates. According to reports, smallpox and human monkeypox share many of the same clinical symptoms. The representative strains of the monkeypox virus from the Congo Basin, Zr-599, and West Africa, Liberia, are utilized [88-92]. According to the A-type inclusion body gene sequence, Zr-599, which was isolated from a patient in the Democratic Republic of the Congo, and Liberia, which was isolated from a patient who had human monkeypox in Liberia, are allocated to the Congo Basin and the West African clades, respectively. To produce the virus solution for the challenge experiments, Vero E6 cells infected with each strain of the monkeypox virus are disrupted in a sonicator (TITEC Ultra S Homogeniser UP-5) for 30 seconds at maximum power. This is followed by high-speed centrifugation (3500 r.p.m. for 5 minutes at 4°C). The plaque assay was used to calculate the virus's infectious dosage. As previously described, the whole suite of vaccinia virus proteins was used as an antigen in an ELISA assay to evaluate antibody levels specific to the virus [93-96]. Limited research data are available on Strain-Specific monkeypox vaccines, therefore, developing customized vaccines and treatments is hampered by the lack of information regarding the impact of various monkeypox vaccines clades on host immunity and vaccine efficacy. Inadequate data about genetic variation and insufficient data about how host genetic variables affect disease severity, and genetic variations in monkeypox vaccines may play a role in the pathogen's pathogenicity and immune evasion [97, 98]. Furthermore, inadequate infrastructure and resources are a problem in many monkeypox vaccines-affected areas, which affects the efficiency of outbreak response and management [99, 100]. Conduct Research Specific to Strains: To develop vaccines and treatments that are specifically targeted, investigate the immunological variations across MPXV clades and how they affect vaccination efficacy [101]. Examine Host Genetic variants: To gain a better understanding and control of the disease, investigate how host genetic variants impact exposure to and immune responses from MPXV. In order to better support epidemic response and prevention initiatives, strengthen public health infrastructure by investing in

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high-risk locations. Encourage Global Collaboration: To accomplish monkeypox vaccine research and guarantee successful disease control plans, exchange information and resources worldwide [102].

CONCLUSIONS

In summary, an examination of the monkeypox virus from the perspectives of genetic variation and host immunity reveals a complicated interaction that determines the severity of the disease and how long it takes to spread. The fate of monkeypox was largely determined by the immunological response, with individual heterogeneity affecting susceptibility and development. The wide range of clinical symptoms and difficulties in controlling outbreaks were attributed to genetic characteristics in both the virus and the host. As science progresses, combining knowledge from immunology and genetics will be essential for creating vaccines and tailored treatments that will eventually improve our capacity to contain and eradicate monkeypox. Further research into these areas will help us better understand monkeypox and develop response plans for new viral dangers in a world that was changing quickly.

Authors Contribution

Conceptualization: FH

Methodology: FH

Formal analysis: MUH

Writing, review and editing: IS, AQ, AH, SR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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