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Immune response to lumpy skin disease virus: Host-virus interactions and immunopathogenesis

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Abstract
Lumpy skin disease (LSD) is one of the economically devastating transboundary viral disease of cattle, caused by the lumpy skin disease virus (LSDV). Understanding the intricate dynamics of the host-virus interactions and immunopathogenesis during LSDV infection is crucial for devising effective control strategies and developing targeted interventions. This review article presents a comprehensive detail of the immune response elicited by LSDV infection, highlighting the role of both innate and adaptive immunity. The innate immune response is the first line of defense against the virus, mediated by phagocytes and natural killer cells. Subsequently, the adaptive immune response plays a pivotal role in neutralizing the virus through the actions of T cells and B cells, which respond to specific viral antigens. Nevertheless, the complex interactions between LSDV and the host's immune system can sometimes lead to immunopathogenesis, causing significant tissue damage and the characteristic skin nodules observed in affected animals. A comprehensive understanding of these immunological aspects holds promise for the development of targeted therapeutic interventions and novel vaccine strategies against LSDV with potential implications for livestock health, welfare, and global food security. By shedding light on the immune responses and their consequences, this review aims to provide insights into the immunological basis of lumpy skin disease and contribute to advancements in its management and control.

Keywords: LSDV, host-virus interactions, immunity, immunopathogenesis

1. Introduction
Lumpy Skin Disease (LSD) is a viral disease that affects cattle, causing significant economic losses and impacting animal welfare. The disease is caused by the Lumpy Skin Disease virus (LSDV), a large double-stranded DNA virus belonging to the Capripoxvirus genus and is closely associated with related diseases like sheep pox and goat pox (Gumbe, 2018) [10]. LSD primarily affects cattle, although it can also infect water buffalo, yaks, and certain wild ruminants (Badhy *et al*., 2021) [5]. The characteristic sign is formation of skin nodules all over the surface of the body Nodules can vary in size and may be accompanied by other clinical signs such as fever, reduced milk production, anorexia, and decreased fertility. Severe cases can lead to generalized disease, with extensive skin lesions, secondary infections, and high mortality rates (Babiuk *et al*., 2008; OIE, 2008) [3, 19].

The first case of LSD was reported in 1929 in Zambia (MacDonald, 1931) [16], LSD is considered endemic in various regions of Africa, including sub-Saharan Africa. Currently, the only African nation still regarded as free of the illness are Libya, Algeria, Morocco, and Tunisia. Over time, the virus has become more virulent, leading to extensive epidemics and pandemics in Africa (Rweyemamu *et al*., 2000) [20]. The disease extended its spread to Middle east countries and also identified in several Asian countries and the disease is broadened to several south east Asian countries Parts of Asia, including India, Pakistan, Bangladesh, and Nepal, have experienced LSD outbreaks. (Das *et al*., 2021) [8]. In India, the Mayurbhanj district of Odisha witnessed initial LSD outbreaks. Out of 2539 susceptible animals, 182 were clinically affected, which resulted in an apparent morbidity rate of 7.1% with no reported deaths. Among the affected districts, Kendrapara had a morbidity rate of 0.75%, whereas Cuttack had the highest rate at 38.34%. (Sudhakar *et al*., 2020) [28].

The principal mode of transmission of LSDV is by biting arthropods like Stomoxys (stable flies), mosquitoes and ticks. Direct contact with infected animals, contaminated fomites, and iatrogenic transmission through improper use of needles or equipment can contribute to disease spread. Factors such as movement of infected animals, international trade and climate change can influence the geographic distribution and epidemiology of LSD (Tuppurainen *et*

al., 2015; Tuppurainen *et al.*, 2013a) [30, 29]. The virus primarily targets epithelial cells, endothelial cells, and certain immune cells, causing cell damage, inflammation, and the formation of characteristic skin nodules (All-Salihi, 2014) [1]. The immunopathogenesis of LSD involves complex interactions between the virus and the host immune system, leading to the recruitment of immune cells, cytokine production, and tissue damage (Tuppurainen *et al*., 2005) [30].

Laboratory diagnosis of LSD relies on a combination of clinical signs, histopathology, and laboratory tests. Direct methods include virus isolation, electron microscopy, and PCR-based techniques for detecting LSDV genetic material. Serological tests, such as enzyme-linked immunosorbent assays (ELISA) are used for antibody detection in the infected animals. (Tuppurainen *et al*., 2011) [32]. Control measures for LSD focus on implementing strict biosecurity measures, vector control, and prompt diagnosis and isolation of infected animals. Vaccination plays a crucial role in LSD control. Live attenuated vaccines or inactivated vaccines are used to induce protective immunity against LSDV. (Najith, 2022) [18].

Understanding the immune response to LSDV is crucial for the development and improvement of vaccines. Effective vaccines stimulate a robust and protective immune response against the virus. By studying the immune response, one can point out the specific components of the immune system that contribute to protection. This knowledge aids in the design and evaluation of vaccines, including determining the optimal antigens, delivery systems, and immunization strategies. By studying the immune responses of vaccinated and naturally infected animals, one can correlate specific immune parameters (e.g., antibody titers, cellular immune responses) with protection from disease or reduction in virus replication. These studies can serve as surrogate markers for vaccine efficacy and guide vaccine development programs. Studying the immune response to LSDV also provides insights into the immunopathogenesis of the disease. It helps understand the interplay between host immune system and virus leading to the observed clinical manifestations, tissue damage and disease progression. (Sudhakar *et al*., 2020 and Hamdi *et al*., 2021) [28, 11].

2. Immune response to LSDV

2.1 Innate immune response to LSDV

During the initial phases of Lumpy Skin Disease Virus (LSDV) infection, the innate immune response holds significant importance. The innate immune system identifies LSDV by employing pattern recognition receptors (PRRs). Upon identifying LSDV, both infected cells and adjacent cells initiate the production and release of type I interferons (IFN-α and IFN-β). These type I interferons establish an antiviral state in neighbouring cells, which confines the virus's spread and triggers the activation of NK cells. Once activated, NK cells possess the ability to directly eliminate virus-infected cells and secrete antiviral cytokines, including interferon-gamma (IFN-γ). (Smith *et al.*, 2018) [26]. Infected cells and virus particles are recognized by macrophages, leading to phagocytosis and subsequent degradation of the virus. Macrophages also produce pro-inflammatory cytokines (Chiu *et al.*, 2016) [7]. LSDV infection also triggers the activation of dendritic cells initiating the adaptive immune response (Ma *et al*., 2019) [15]. Infection with LSDV triggers an inflammatory reaction marked by the discharge of pro-inflammatory cytokines and chemokines. (McNab *et al*., 2015) [17]. These innate immune mechanisms contribute to limiting viral replication initiating adaptive immune responses and shaping the overall immune response to LSDV infection.

2.2 Adaptive immune response to LSDV

2.2.1 Humoral immune response to LSV

B cells, via their surface B cell receptors (BCRs), recognize specific LSDV antigens. Co-stimulatory signals provided by activated T cells (primarily CD4+ T cells) and gets activated. Activated B cells differentiate into plasma cells, specialized cells producing large amounts of antibodies (also known as immunoglobulins, Igs). Antibodies produced by plasma cells target specific LSDV antigens. LSDV-specific antibodies bind to the virus, preventing its entry into host cells and neutralizing its infectivity. Antibodies can coat LSDV particles, facilitating their recognition and uptake by phagocytic cells (e.g., macrophages), leading to virus clearance.

2.2.2 Cell-mediated immune response to LSDV

The role of cell-mediated immunity (CMI) in LSD is poorly understood (Tuppurainen *et al.*, 2017; Xu *et al*., 2004; Kennedy *et al.*, 2009) [31, 34, 13]. The first indication of CMI was reported back when delayed-type hypersensitivity (DTH) was observed (Carn *et al*., 1995) [6]. CMI primarily mediated by T lymphocytes involved in production of key cytokines (Smith *et al*., 2018) [26]. Antigen-presenting cells, particularly dendritic cells, capture LSDV antigens and present them to T cells. T cells with specific TCRs that can recognize LSDV antigens become activated upon binding to the presented antigens. Co-stimulatory molecules, such as CD80 and CD86 on antigen-presenting cells, interact with CD28 receptors on T cells, providing additional signals for T cell activation. Upon activation, CD4+ T cells differentiate into subsets such as T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), and regulatory T cells (Tregs).Th1 cells produce interferon-gamma (IFN-γ) and other pro-inflammatory cytokines, promoting cellular immune responses and activating macrophages to eliminate LSDV-infected cells (Schroeder *et al*., 2010) [22] Th2 cells secrete cytokines that stimulate B cells to produce antibodies, contributing to humoral immune responses.Th17 cells participate in inflammatory responses and tissue repair processes. Treg cells help regulate and suppress excessive immune responses, preventing immune-mediated damage.CD8+ T cells differentiate into CTLs, which recognize and directly kill LSDV-infected cells through the recognition of viral peptides presented on infected cells major histocompatibility complex (MHC) class I molecules. (Luckheeram *et al*., 2012) [14].

2.3 Generation of Memory Cells

After the successful clearance of LSDV infection, the body produces a reservoir of memory T cells and memory B cells. These memory T cells and B cells offer extended immunity and a swift reaction upon encountering LSDV again, resulting in a more effective and precise immune response.

The adaptive immune reaction to LSD is pivotal in managing and eliminating LSDV infection. This process entails triggering T cells and B cells, leading to their specialization into effector subsets, the synthesis of antibodies, and the establishment of memory cells. This orchestrated adaptive immune response aids in forming safeguarding immunity against LSDV and offers enduring immunological

recollection to counter prospective LSDV infections.

3. Immune Evasion strategies

Lumpy Skin Disease Virus (LSDV) has evolved several mechanisms to evade or modulate host immune responses, allowing the virus to persist and cause disease. Some of the mechanisms employed by LSDV

3.1 Interference with Interferon Response

LSDV produces proteins that interfere with the production and signalling of type I interferons (IFNs), particularly interferon-alpha (IFN-α) and interferon-beta (IFN-β). These viral proteins can inhibit the induction of IFNs by blocking key signalling pathways or suppressing the expression of interferon-stimulated genes (ISGs), which are involved in antiviral defence. (Smith *et al*, 2013) [25]

3.2 Inhibition of Apoptosis

LSDV encodes proteins that prevent or delay programmed cell death (Apoptosis), which is a critical antiviral defence mechanism. By inhibiting apoptosis, LSDV can prolong infected cell survival, allowing for sustained viral replication and spread (Hay *et al*., 2002) [12]

3.3 Immune Evasion Proteins

LSDV generates specific proteins that directly hinder the host's immune response. Certain viral proteins have the capacity to disrupt the presentation of antigens by obstructing the expression of major histocompatibility complex (MHC) class I molecules on infected cells or by intervening with pathways related to antigen processing and presentation. These tactics of evasion undermine the immune system's capability to identify and remove cells that are affected by LSDV. (Senkevich and Moss, 1998) [24].

3.4 Modulation of Host Cytokine Response

LSDV can manipulate host cytokine responses, influencing the balance between pro-inflammatory and anti-inflammatory cytokines. The virus may suppress the production of pro-inflammatory cytokines, such as interferons and interleukins, while promoting the secretion of anti-inflammatory cytokines. This modulation can dampen the immune response, impairing the recruitment and activation of immune cells necessary for effective viral clearance (Alcami *et al*., 2003) [2].

3.5 Immune Modulation of Infected Host Cells

Within infected cells, LSDV has the ability to manipulate host immune responses. This manipulation might involve modifying the activity of host genes related to immune signaling pathways or the activation of immune cells. These changes can impact the host's reaction to the infection, potentially weakening the antiviral immune response (Seet *et al*., 2003) [23].

4. Immunopathogenesis of LSDV

Lumpy Skin Disease Virus (LSDV) infection can lead to various immunopathological consequences, which are the results of interplay between virus and the host. These immunopathological consequences contribute to the clinical manifestations and tissue damage observed in affected animals LSDV infection triggers an inflammatory response characterized by the release of pro-inflammatory cytokines, (IL-1, IL-6, TNF-α) (Samojlovic *et al*., 2019) [21]. The inflammatory response serves as a host defence mechanism, aiming to eliminate the virus. However, excessive or prolonged inflammation can lead to tissue damage and contribute to disease pathology. LSDV infection leads to the formation of characteristic skin nodules and lesions. The formation of these lesions involves the infiltration of immune cells, (Fay *et al*., 2022) [9]. The immunopathological consequences within these lesions include the accumulation of immune cells, tissue remodelling, and the development of fibrosis (Babiuk *et al*., 2009) [4] LSDV infection can cause tissue damage and ulceration, particularly in the skin and mucous membranes. The immunopathological consequences of tissue damage include the destruction of infected cells, disruption of tissue architecture and impairment of normal tissue function. LSDV infection possesses the capacity to induce systemic impacts on diverse organs and tissues, extending beyond the initial site of infection. The virus can spread to various organs, triggering inflammation, harm to tissues, and possible impairment in their functionality. The release of pro-inflammatory cytokines can also contribute to the manifestation of systemic effects. and other immune mediators into the bloodstream. LSDV-induced immunosuppression can make infected animals more susceptible to secondary infections. In situations where the immune system is weakened, opportunistic pathogens can exploit this vulnerability, potentially resulting in the emergence of secondary bacterial, fungal, or viral infections. Secondary infections can exacerbate the immunopathological consequences and disease severity. (Samojlovic *et al*., 2019) [21].

5. Conclusion

Understanding the immunopathological consequences of LSDV infection is important for developing targeted therapies, interventions and for control of the disease. By elucidating the underlying mechanisms, researchers can identify potential targets for therapeutic interventions, design strategies to mitigate tissue damage, and enhance the host immune response for effective viral clearance.

6. Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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