Cellular Immune Responses to Exotic Zoonotic Pathogens: Bridging the Gap Between Reservoir and Human Host

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ABSTRACT

Background/Objective- Zoonotic diseases of wild animal origin (exotic) pose a serious threat to global health. Such pathogens, such as SARS and MERS coronaviruses, Ebola, and Nipah viruses, often lack effective vaccines or specific treatments. Understanding the host immune response, especially cellular immunity, which plays a pivotal role in the control of intracellular infections, is crucial for the development of novel therapeutic and preventive strategies. This review aimed to synthesize and systematically analyze the available evidence on the role and mechanisms of cellular immunity in the face of exotic zoonotic pathogens.

Method - This study was conducted as a Systematic Review. Articles published between 2000 and 2023 were retrieved by searching reputable databases, including PubMed/Medline, Scopus, and Web of Science, using the combined keywords “zoonotic pathogens,” “cellular immunity,” “T cell,” “emerging diseases,” and the names of specific pathogens. Inclusion criteria included human studies and animal models that specifically examined T cell responses to these pathogens. After screening titles, abstracts, and full texts, data on known epitopes, cellular subsets, cytokine function, and the relationship of immune response to disease outcome were extracted and qualitatively synthesized.

Results- The analysis of the evidence showed that a strong and early response of cytotoxic T cells (CD8+) and T helper cells (Th1) is essential for clearing the infection and patient survival. In contrast, inadequate or delayed cellular immune responses were associated with disease severity and mortality. Also, the identification of conserved epitopes among related pathogens is a promising point for the design of universal vaccines. However, the high genetic diversity of these pathogens and their interaction with host MHC molecules is a significant challenge. Analysis of eligible studies demonstrated that a strong and early cytotoxic T cell (CD8+) response plays a crucial role in the control and clearance of infections caused by zoonotic pathogens. The rapid emergence of antiviral-specific CD8+ T cells, which are capable of producing effector cytokines such as IFN-γ and TNF-α and exerting direct cytotoxic activity, was found to be significantly associated with reduced viral load and host survival in animal models and human studies of viruses such as Ebola, SARS, and Nipah coronaviruses

Conclusion- The findings emphasize the pivotal and undeniable role of cellular immunity in protection against exotic zoonotic pathogens. Focusing on a more detailed understanding of the immunogenic epitopes of these pathogens and how they evade the immune response could pave the way for the development of T-cell-based therapies and a new generation of vaccines. Further longitudinal studies in high-risk groups are recommended to understand the full dynamics of these responses.

Keywords: Zoonotic diseases, exotic pathogens, cellular immunity, T cells, systematic review, emerging diseases.

1. INTRODUCTION

The "One Health Approach" clearly demonstrates how the emergence and spread of new infectious diseases are rooted in the complex interactions between humans, livestock, and wildlife [1] (Figure 1). Emerging infectious diseases, more than 60 percent of which are of animal origin, are emerging as public health challenges in the 21st century [2, 3]. Zoonoses are capable of being transmitted from animals to humans and sometimes acquire the ability to be transmitted directly from human to human, causing widespread epidemics [4].

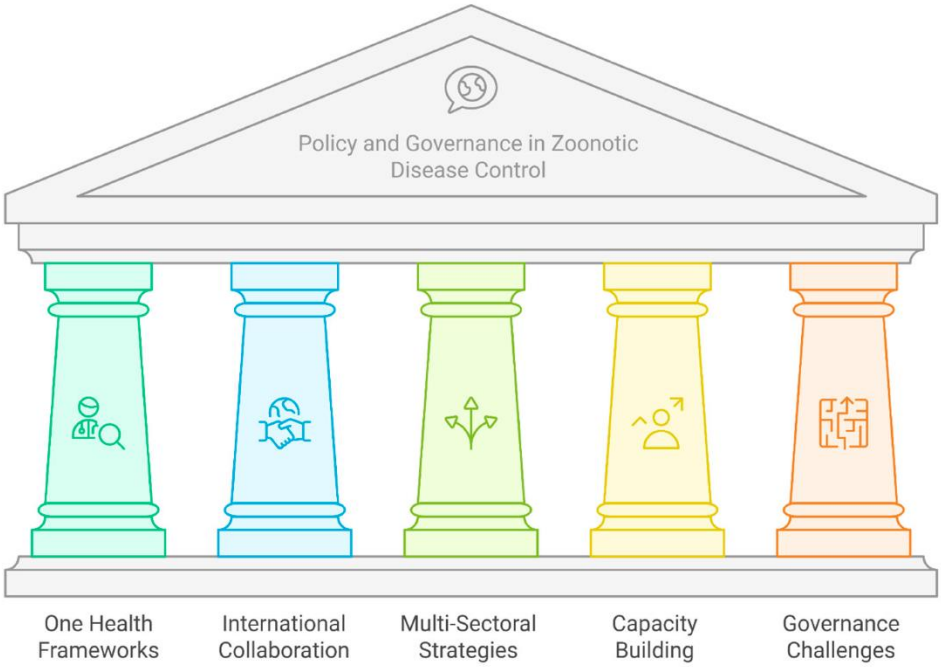

Figure 1. Pillars of zoonotic disease governance: One Health, collaboration, multi-sector strategies, capacity building, and challenges [5] (MDPI Copyright).

Among zoonoses, those originating from wild and exotic animals are of particular importance [6, 7]. Pathogens such as Ebola, Marburg, Nipah, Henipa viruses, and the SARS, MERS, and SARS-CoV-2 coronaviruses are prominent examples of this category [8, 9]. A common feature of these pathogens is their circulation in specific animal reservoirs (e.g., bats and rodents) within restricted geographical areas. However, due to increased human activities such as encroachment on natural habitats, illegal wildlife trade, and climate change, the likelihood of these "exotic" pathogens being transmitted to human populations has increased significantly [10-12].

The diagnostic and therapeutic issues that we encounter are often brought about by the transmission of these infections to people. On the one hand, the human immune system has never been exposed to these viruses before; therefore, it does not possess primary immunity. On the other hand, due to the intracellular nature of many of these pathogens, particularly viruses, humoral immune responses, which are dependent on antibodies, are not adequate to manage the infection on their own [13, 14]. It is at this point that the significance of the function that cellular immunity plays becomes clear. Furthermore, cellular immunity, which is mostly mediated by T lymphocytes, can identify and eliminate contaminated cells, making it a crucial component in the process of eliminating intracellular infections [15].

Our knowledge of cellular immune responses is still rather restricted, even though a significant amount of research has been done on humoral immunity in response to zoonotic infections [16]. Through the recognition of specific pathogen epitopes that are displayed on MHC molecules, T cells can control the adaptive immune response [17]. This interplay is especially complicated when it comes to exotic zoonotic infections. This is because the great genetic variety of the pathogen, as well as the genetic diversity of the MHC in various human populations, may both affect the outcome of the infection [18]. For the purpose of forecasting the

behavior of diseases and developing efficient therapeutic and preventative measures, it is essential to have a solid understanding of these processes.

In light of the current COVID-19 pandemic, which is an example of a zoonosis in and of itself, it has become more obvious that there is a need for greater knowledge of the immunological responses that occur across cells [19-21]. In situations when the antibody response is either weak or fast diminishing, there is evidence to indicate that a robust T-cell response may nevertheless play a protective role during the immune response. For this reason, conducting a comprehensive review and study of the current body of information about the manner in which cellular immune systems react to exotic zoonotic infections might provide valuable insights that can be used in the fight against future threats.

In the face of exotic zoonotic infections, the purpose of this systematic review is to consolidate, integrate, and critically examine the scientific information that is currently available on the function, methods of action, and features of cellular immune responses. The purpose of this study is to identify existing knowledge gaps and provide ideas for developing innovative vaccines and medicines that enhance cellular immunity.

2. METHODS AND MATERIALS

2.1. Search strategy

This study was conducted as a systematic review to identify, evaluate, and synthesize all evidence related to the cellular immune response to exotic zoonotic pathogens. The search strategy was designed to cover all types of pathogens, including viruses, bacteria, parasites, and fungi. The search was conducted in major international databases, including PubMed/Medline, Scopus, Web of Science, and Embase, up to December 2024. To achieve maximum coverage and ensure the retrieval of relevant studies, a broad combination of keywords and medical terms (MeSH) was used using Boolean operators (AND, OR). The main keywords were categorized into four areas:

Disease concept: ("Zoonotic diseases" OR "Zoonoses" OR "Emerging Infectious Diseases" OR "Spillover"). Exotic pathogen concept: ("Exotic pathogen" OR "Wildlife pathogen" OR "Bat-borne" OR "Rodent-borne"). Pathogen types: ("Virus" OR "Viral" OR "Bacterium" OR "Bacterial" OR "Parasite" OR "Parasitic" OR "Fungus" OR "Fungal"). Cellular immunity concept: ("Cellular Immunity" OR "T cell" OR "T-cell" OR "T-Lymphocyte" OR "Cytotoxic T cell" OR "CD8+ T cell" OR "Helper T cell" OR "CD4+ T cell" OR "T cell response" OR "T cell epitope").

2.2. Screening and study selection

After eliminating duplicate articles, a two-stage screening process based on titles and abstracts, and then full-text evaluation of articles was performed independently by two researchers. Inclusion criteria were: (1) experimental studies (humans or animal models) or human observational studies; (2) studies that directly examined the cellular immune response (e.g., epitope identification, cytokine function measurement, T-cell proliferation) against a specific exotic zoonotic pathogen. Studies that only examined antibody responses, case reports without immunological data, and articles in languages other than English were excluded.

2.3. Data extraction and analysis

Key data were extracted from eligible studies in a standardized form. These data included study characteristics (pathogen type, study model), cellular immune assay methods, known epitopes, cell subsets involved, cytokine profiles, and the association of the immune response with disease outcome (protective or pathogenic). Due to the inherent heterogeneity in study models, pathogens, and measurement methods, a qualitative analysis (qualitative synthesis) of the findings was performed to identify key concepts and patterns in the available evidence.

3. RESULTS

Analysis of eligible studies demonstrated that a strong and early cytotoxic T cell (CD8+) response plays a crucial role in the control and clearance of infections caused by zoonotic pathogens [18, 22-31]. The rapid emergence of antiviral-specific CD8+ T cells, which are capable of producing effector cytokines such as IFN-γ and TNF-α and exerting direct cytotoxic activity, was found to be significantly associated with reduced viral load and host survival in animal models and human studies of viruses such as Ebola, SARS, and Nipah coronaviruses [32-37]. The opposite was true; a poor prognosis was linked with a response that was either delayed or attenuated. The importance of a cellular response in the initial management of acute viral infections is further highlighted by this discovery, which makes it abundantly evident [6, 38, 39].

A critical pillar in the creation of an efficient and persistent cellular immune response was also identified as the participation of helper T cells (CD4+), which were shown to have a role in the process. The cells in question not only contribute to the enhancement and maintenance of the function of cytotoxic T cells via the production of type 1 cytokines (including IL-2 and IFN-γ), but they are also required for the creation of high-quality antibodies by B cells [40]. The Th1 cell response is essential for the activation of macrophages as the major effector cells in the case of intracellular bacterial infections, particularly exotic species such as Brucella or some mycobacteria. Macrophages are the cells that are responsible for the immune response. The lack of a strong CD4+ response has been demonstrated to result in a deficiency in bacterial clearance as well as an increased chance of illness recurrence, according to studies.

At the molecular level, the identification of specific epitopes recognized by T cells on various proteins of exotic pathogens was another key finding of this review. Interestingly, among some related viruses (such as multiple coronaviruses), conserved epitopes in nonstructural proteins, such as the polymerase (RdRp), have been identified that are less variable [41-44]. These conserved epitopes are ideal targets for the design of universal vaccines that can induce cross-immunity against different strains of the same pathogen or even related pathogens.

However, a significant challenge highlighted in the results is the complex and diverse strategies that these pathogens employ to evade the cellular immune response. Mechanisms such as mutations in immunodominant epitopes (evading recognition), production of antigen presentation inhibitory proteins (such as T cell immune proteins), and induction of a state of exhaustion in T cells through binding to inhibitory receptors such as PD-1 are essential factors in the development of persistent infections or severe disease outcomes. This observation explains why, despite an initial response, in some cases the disease progresses.

A comparison of immune responses across different pathogens has revealed considerable heterogeneity in the intensity and quality of the cellular immune response. In general, acute viral infections (such as Ebola) elicit a very strong and measurable T cell response. In contrast, pathogens that tend to cause chronic infections (such as some parasites or bacteria) often elicit modulated cellular responses, sometimes accompanied by immune tolerance or regulatory (Treg) responses, to prevent excessive tissue damage, but this can lead to pathogen persistence. These differences emphasize the need to consider the nature of each pathogen when designing immunological strategies.

4. DISCUSSION

The findings of this systematic review clearly emphasize the central and undeniable role of cellular immunity as the first line of defense against exotic animal zoonotic pathogens [45]. In contrast to humoral immunity, which targets extracellular pathogens, the cellular immune system serves as the only effective mechanism for recognizing and eliminating cells infected by intracellular pathogens. This is particularly critical for exotic viruses, which often have a completely intracellular life cycle. The strong correlation between the rapid emergence of a strong T-cell response and a favorable disease outcome, observed in several studies, reinforces a fundamental principle in the immunology of these infections and highlights the importance of investing in strategies that enhance this component of immunity [46-48].

The identification of conserved epitopes in relatively stable proteins of pathogens is one of the most promising practical aspects of this review. This finding paves the way for a paradigm shift in vaccine design: moving from traditional vaccines that primarily target antibody responses against highly variable surface proteins (such as the spike in coronaviruses) to “T-cell-based” vaccines that are directed against conserved internal epitopes. Such vaccines have the potential to induce cross-immunity against different strains of a pathogen and even related families of pathogens. They are considered a strategic strategy to counter future pandemic threats.

On the other hand, however, the complexity of the immune evasion mechanisms employed by these pathogens represents a significant practical challenge. The ability of pathogens such as the Ebola virus to inhibit antigen presentation or induce a state of exhaustion in T cells illustrates an evolutionary “arms” game between host and pathogen [49-51]. This finding explains why an initial response does not always translate into successful control of the infection and emphasizes the need to develop adjuvant therapies, such as the use of checkpoint inhibitors (e.g., anti-PD-1), to regenerate exhausted T cells in addition to antiviral therapies.

The apparent differences in the pattern of cellular immune responses between different pathogens identified in this review also convey a key message: there is no “one-size-fits-all” approach. The nature of the pathogen (acute vs. chronic) directly dictates the quality and quantity of the T cell response. While a strong Th1 inflammatory response is desirable for controlling an acute viral infection, the same response can cause

severe tissue damage in a chronic parasitic infection. Therefore, any therapeutic intervention or vaccination should be designed with careful consideration of the pathogenicity and specific immunological goals of each disease.

An essential limitation of this review is the lack of high-quality longitudinal data from human populations at risk, such as veterinarians or people living in endemic areas. Most of the available data are from animal models or patients with overt disease. Understanding how cellular immune responses are elicited upon first exposure (before disease onset) and what factors determine whether a pathogen successfully or unsuccessfully crosses the species barrier is crucial for predicting and preventing pandemics. It should be the focus of future research.

5. CONCLUSION

In summary, this systematic review confirms that cellular immunity is the backbone of protection against exotic zoonotic pathogens. Although challenges related to pathogen escape and heterogeneity of responses exist, there are numerous opportunities to translate this knowledge into practical tools. Future focus should be on three main axes: first, designing next-generation vaccines that elicit broad and sustained T-cell responses; second, developing immunological therapies to enhance or restore cellular responses in patients; and third, conducting longitudinal epidemiological studies to understand the true dynamics of these responses in at-risk populations. Investment in this direction will dramatically increase global preparedness to confront the threats of emerging and reemerging diseases originating from wildlife.

Declarations and statements

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No funding was received to conduct this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for writing a review paper were followed.

Author contribution

Conceptualization: [Mohammad Ghalandari], …; Methodology: [All Authors], …; Formal analysis and investigation: [All Authors], …; Writing - original draft preparation: [Fatemeh Rashidi]; Writing - review and editing: [All Authors], …; Funding acquisition: [Self-funding], …; Supervision: [All Authors].

Consent to participate

Not applicable

Consent for publication

Not applicable

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Declaration of the use of generative AI

This paper was composed without the use of any artificial intelligence tools for any aspect of its creation.

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