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Human Immune Response to Mosquito-Borne Pathogens: Mechanisms and Implications

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Abstract Mosquito-borne diseases, such as malaria, dengue, and Zika, pose a significant global health threat due to their widespread prevalence and severe consequences. This study investigates the intricate mechanisms of human immune responses to mosquito-borne pathogens, focusing on both innate and adaptive immunity. The role of pattern recognition receptors, inflammatory pathways, and cytokine signaling in initial pathogen detection is explored, alongside the limitations of innate immunity. The adaptive immune response, encompassing B cell-mediated antibody production and T cell functionality, is analyzed, with attention to the challenges posed by immunopathology. A case study on Plasmodium highlights the immune evasion strategies employed by pathogens, emphasizing antigenic variation and immune suppression. The implications of these findings for vaccine development and therapeutic interventions are discussed, underscoring current progress and challenges in achieving long-term immunity. Finally, the study identifies future research directions, advocating for systems immunology and innovative technologies to enhance our understanding of host-pathogen interactions. This research provides a comprehensive framework for leveraging immune responses in combating mosquito-borne diseases and improving global health outcomes.
Keywords Mosquito-borne diseases; Immune response; Pathogen evasion; Vaccine development; Systems immunology

1 Introduction

Mosquito-borne diseases represent a significant global health challenge, particularly in tropical and subtropical regions. These diseases, including malaria, dengue fever, chikungunya, yellow fever, Zika virus infection, and West Nile virus infection, are transmitted through the bites of infected mosquitoes and have emerged as major health burdens (Ngono and Shresta, 2018; Bhattacharjee et al., 2023; Zoladek and Nisole, 2023). The geographical distribution of mosquito vectors has expanded dramatically, increasing the global reach of these pathogens and posing a constant threat of emergence and re-emergence (Baxter et al., 2017). The impact of these diseases is profound, leading to severe morbidity and mortality, and placing a heavy burden on healthcare systems worldwide (Samuel et al., 2018).

Understanding the human immune response to mosquito-borne pathogens is crucial for developing effective therapeutic and preventive strategies. The initial interaction between the pathogen and the host immune system often occurs at the site of the mosquito bite, where innate and adaptive immune responses are triggered (Cantaert et al., 2023; Rabinovich-Ernst et al., 2023). These responses play a critical role in determining the outcome of the infection, influencing both the establishment of the pathogen and the progression of the disease. Moreover, mosquito-borne pathogens have evolved various mechanisms to evade the host immune system, complicating the development of effective treatments and vaccines (Bhattacharjee et al., 2023; Zoladek and Nisole, 2023). By elucidating the molecular and cellular mechanisms of these immune responses, researchers can identify potential targets for novel therapeutics and vector-targeted vaccine candidates (Wang et al., 2019; Elrefaey et al., 2021).

This study attempts to explore the mechanisms of the human immune response to mosquito-borne pathogens and their implications for disease control and prevention, discuss the roles of innate and adaptive immune responses at the site of mosquito bites in the establishment and progression of infection, and provide an overview of key immune genes, cell types, and pathways involved in the human response to mosquito bites and pathogen

inoculation. Additionally, it explores the strategies employed by mosquito-borne pathogens to evade the host immune system and their impact on disease outcomes, while informing the development of novel therapeutics and vector-targeted vaccines to disrupt vector-mediated disease transmission. Through these efforts, the study aims to advance our understanding of the complex interactions between mosquito-borne pathogens and the human immune system and contribute to more effective strategies for controlling and preventing these diseases.

2 Mosquito-Borne Pathogens and Their Interaction with the Human Immune System

2.1 Overview of major mosquito-borne pathogens

Mosquito-borne pathogens such as dengue virus (DENV), malaria parasite, and Zika virus (ZIKV) are significant global health threats (Wang, 2024). DENV, a member of the Flaviviridae family, is responsible for the most prevalent mosquito-borne viral diseases, with four serotypes causing a range of symptoms from mild fever to severe hemorrhagic fever (Ngono and Shresta, 2018; Rathore and St. John, 2018). ZIKV, also a flavivirus, gained global attention due to its association with congenital Zika syndrome and its rapid spread in the Americas (Hamel et al., 2015). Malaria, caused by Plasmodium parasites, remains a major cause of morbidity and mortality, particularly in tropical regions (Bhattacharjee et al., 2023).

2.2 Pathogen-specific entry mechanisms and initial immune evasion strategies

Each pathogen employs unique mechanisms to enter host cells and evade the immune system. DENV and ZIKV primarily infect skin cells such as dermal fibroblasts, epidermal keratinocytes, and dendritic cells. DENV uses receptors like DC-SIGN and mannose receptor to facilitate entry, while ZIKV entry is mediated by receptors such as AXL and Tyro3 (Hamel et al., 2015; Rathore and St. John, 2018). Both viruses can manipulate the host's immune response; for instance, ZIKV induces autophagy in skin fibroblasts to enhance replication. Malaria parasites, on the other hand, enter the human body through the bite of an infected Anopheles mosquito, initially infecting liver cells before moving to red blood cells. The parasites evade the immune system by altering the surface proteins of infected red blood cells, making it difficult for the immune system to recognize and destroy them (Bhattacharjee et al., 2023).

2.3 Comparative analysis of immune system challenges posed by these pathogens

The immune challenges posed by these pathogens are multifaceted. DENV and ZIKV both trigger strong innate immune responses, including the production of interferons and activation of T cells. However, they also exploit immune evasion strategies such as antibody-dependent enhancement (ADE), where pre-existing antibodies from a previous infection can facilitate viral entry into host cells, exacerbating the disease (Figure 1) (Samuel et al., 2018; Ngono and Shresta, 2018; Castanha et al., 2020).

This phenomenon is particularly concerning for DENV, where cross-reactive antibodies from one serotype can enhance infection by another serotype. In contrast, malaria parasites evade the immune system through antigenic variation and immune suppression. The parasites can alter the proteins expressed on the surface of infected red blood cells, helping them avoid detection by the immune system. Additionally, malaria can suppress the host's immune response, making it harder for the body to fight off the infection (Bhattacharjee et al., 2023).

Mosquito-borne pathogens such as DENV, ZIKV, and malaria parasites present significant challenges to the human immune system through various entry mechanisms and immune evasion strategies. Understanding these interactions is crucial for developing effective treatments and vaccines. DENV and ZIKV exploit mechanisms like ADE and receptor-mediated entry to enhance their infectivity, while malaria parasites use antigenic variation and immune suppression to evade detection. These insights are vital for advancing therapeutic and preventive measures against these pervasive diseases.

3 Innate Immune Response to Mosquito-Borne Pathogens

3.1 Role of pattern recognition receptors (PRRs) in pathogen detection

Pattern recognition receptors (PRRs) are crucial components of the innate immune system, responsible for detecting conserved molecular structures known as pathogen-associated molecular patterns (PAMPs) and

damage-associated molecular patterns (DAMPs) (Amarante-Mendes et al., 2018; Li and Wu, 2021). These receptors include Toll-like receptors (TLRs), nucleotide oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I-like receptors (RLRs), which are located on the cell surface or within intracellular compartments (Veklich, 2018; Wicherska-Pawłowska et al., 2021). Upon recognizing PAMPs or DAMPs, PRRs initiate signaling cascades that lead to the activation of immune responses aimed at eliminating the pathogens （Figure 2） (Brubaker et al., 2015; Carty et al., 2020). This detection mechanism is essential for the early identification and response to mosquito-borne pathogens, such as viruses and bacteria, ensuring a rapid and effective immune defense (Gulati et al., 2018; Tsolaki et al., 2021).

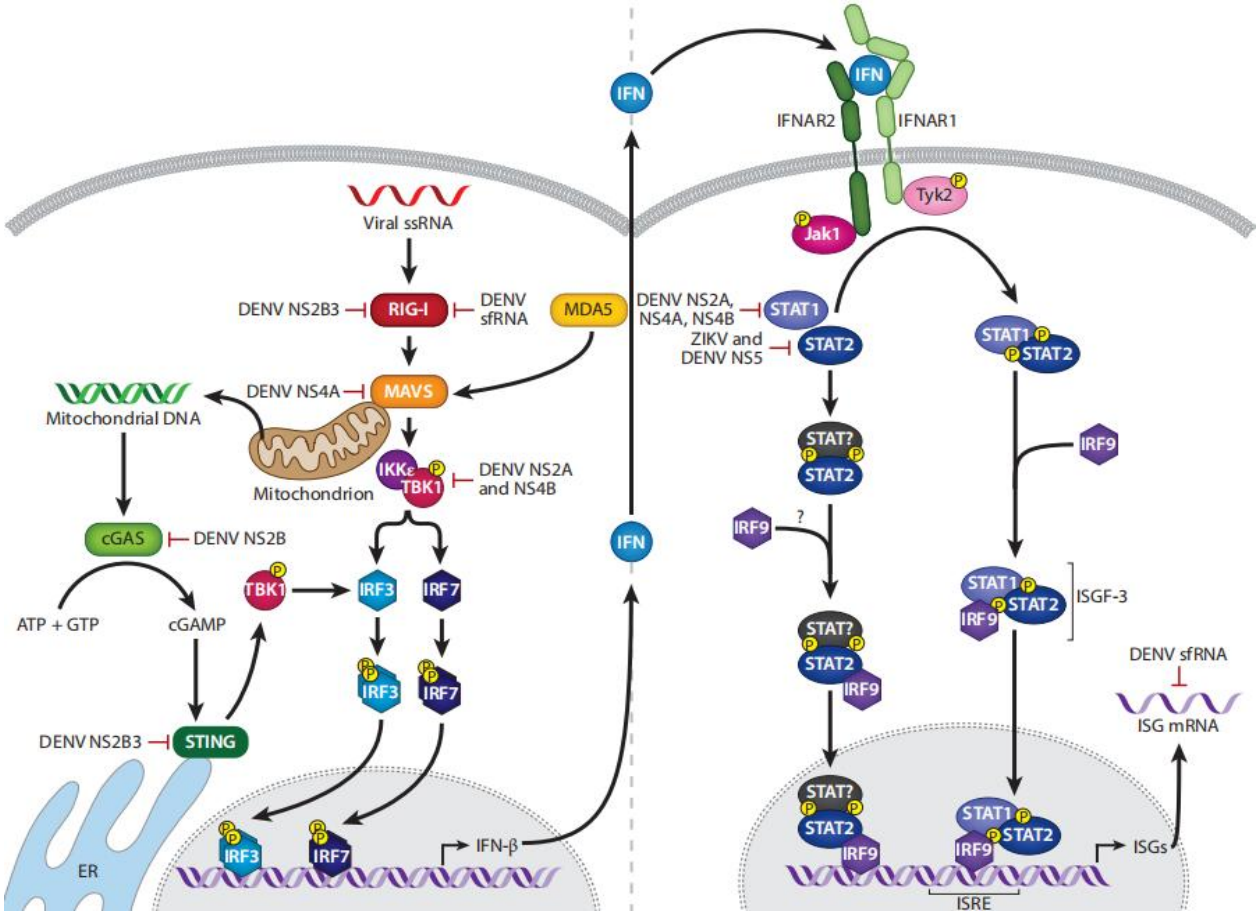

Figure 1 The interferon system (Adopted from Ngono and Shresta, 2018)

Image caption: Following flaviviral infection, viral RNA is sensed by cellular pattern recognition receptors, including RLRs, which induce multiple transcription factors including the IRFs and NF-κB, leading to transcription of interferon. Interferon is secreted and binds the type I interferon receptor to activate the JAK-STAT signal transduction pathway. STAT1 and STAT2 are phosphorylated and form a heterodimer that joins IRF9 to form ISGF-3. The ISGF-3 complex then binds to ISREs in the genome to promote expression of ISGs. DENV may evade the interferon system by multiple mechanisms, including degradation of STAT2, blocking of STAT1 and STAT2 phosphorylation, suppression of STAT1 signaling, blocking of TBK1 phosphorylation, blocking of MAVS binding to RIG-I, induction of mitochondrial elongation linked to viral replication complexes, cleavage of mitochondrial fusion proteins, prevention of RIG-I translocation to mitochondria, binding of TRIM25, cleavage of STING, degradation of cGAS, and inactivation of host RNA-binding proteins. Abbreviations: ER, endoplasmic reticulum; IRF, interferon regulatory factor; ISGF, interferon-stimulated gene factor; ISRE, interferon-stimulated response element; MAVS, mitochondrial antiviral-signaling protein; RLR, RIG-I-like receptor; sfRNA, subgenomic flavivirus RNA; ssRNA, single-stranded RNA (Adopted from Ngono and Shresta, 2018)

3.2 Inflammatory response and cytokine signaling pathways

The activation of PRRs triggers a series of signaling pathways that result in the production of pro-inflammatory cytokines and type I interferons (IFNs) (Carty et al., 2020; Wicherska-Pawłowska et al., 2021). These cytokines, including interleukins (IL-1, IL-6, IL-18) and tumor necrosis factor-alpha (TNF-α), play a pivotal role in

orchestrating the inflammatory response by recruiting and activating various immune cells (Wang et al., 2019). The production of type I and type III IFNs leads to the induction of interferon-stimulated genes (ISGs), which establish an antiviral state within the host cells. This cytokine signaling is crucial for controlling the spread of mosquito-borne pathogens and limiting their replication (Okamoto et al., 2017). However, an excessive inflammatory response can be detrimental, leading to tissue damage and contributing to the pathology of infections.

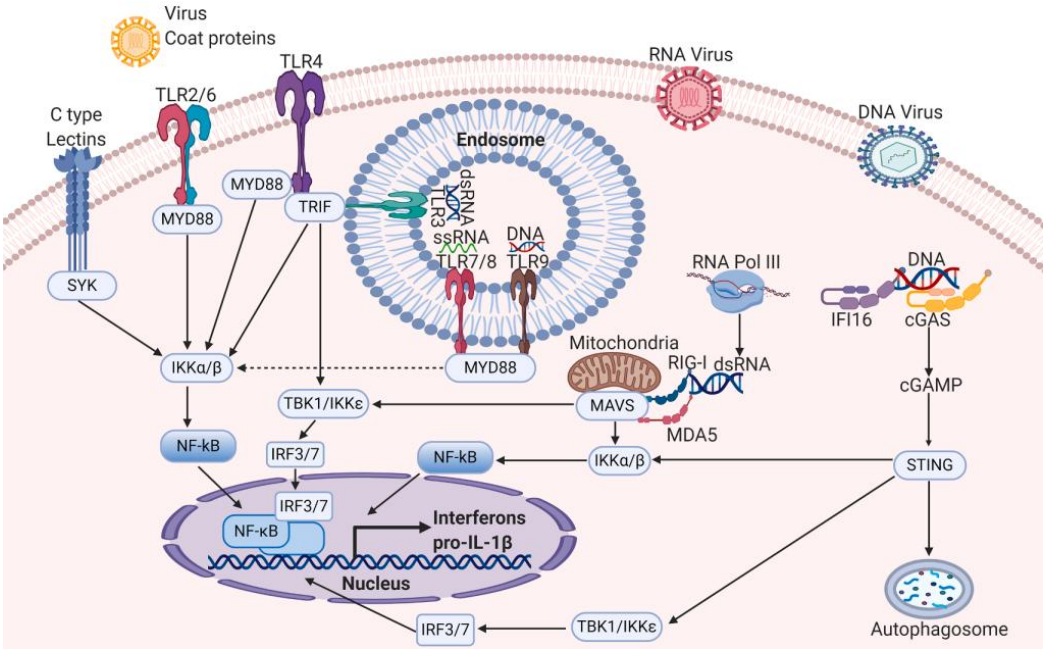

Figure 2 The innate immune system senses viruses using different PRRs (Adopted from Carty et al., 2020)

3.3 Limitations and failures of innate immunity in controlling infections

Despite the critical role of the innate immune system in the initial defense against mosquito-borne pathogens, there are limitations and failures that can compromise its effectiveness. Some pathogens have evolved mechanisms to evade detection by PRRs or to inhibit the signaling pathways activated by these receptors (Veklich, 2018; Tsolaki et al., 2021). For instance, certain viruses can suppress the production of type I IFNs or interfere with cytokine signaling, allowing them to replicate and spread within the host (Okamoto et al., 2017). Additionally, the innate immune response can sometimes be insufficient to completely eliminate the pathogen, necessitating the involvement of the adaptive immune system for a more robust and long-lasting defense (Amarante-Mendes et al., 2018; Li and Wu, 2021). Understanding these limitations is crucial for developing strategies to enhance innate immunity and improve the control of mosquito-borne infections.

The innate immune response to mosquito-borne pathogens is a complex and multifaceted process involving the detection of pathogens by PRRs, the activation of inflammatory and cytokine signaling pathways, and the limitations and failures that can occur in this system. By understanding these mechanisms, researchers can develop better strategies to enhance immune responses and control infections more effectively.

4 Adaptive Immune Response: Mechanisms and Challenges

4.1 Activation and role of B cells and antibody production

B cells play a crucial role in the adaptive immune response to mosquito-borne pathogens by producing antibodies that neutralize the pathogens. For instance, in the context of malaria, skin scarification with a P. falciparum circumsporozoite peptide has been shown to elicit sporozoite-neutralizing antibodies, particularly when combined with specific adjuvants that enhance the immune response (Mitchell et al., 2022). Similarly, a tetravalent dengue vaccine has been demonstrated to induce significant neutralizing antibody responses against all dengue virus serotypes, highlighting the importance of B cell activation in providing protective immunity (Lin et al., 2020).

4.2 T cell-mediated immunity: CD4+ and CD8+ T cell roles

T cells, particularly CD4+ and CD8+ T cells, are pivotal in controlling mosquito-borne viral infections. CD8+ T cells can directly kill infected cells and produce pro-inflammatory cytokines such as IFN-γ and TNF-α, which are essential for controlling viral replication (Tian et al., 2019). CD4+ T cells, on the other hand, assist in the activation of B cells and CD8+ T cells, produce cytokines, and promote the formation of memory responses. In the case of dengue virus infection, CD4+ T cells have been shown to enhance both B cell and CD8+ T cell responses, thereby playing a multifaceted role in the immune defense. Additionally, the immune response to mosquito bites themselves can prime T cells and shift the immune response towards a Th2-driven response, which is crucial for the subsequent activation of CD8+ T cells (Cantaert et al., 2023).

4.3 Immunopathology: when the immune response exacerbates disease severity

While the adaptive immune response is essential for controlling infections, it can sometimes exacerbate disease severity. For example, regulatory T cells (Tregs) can impede effective immune responses in malaria by interfering with T helper cell responses and B cell interactions, thereby delaying parasite clearance and preventing the development of potent adaptive immunity (Kurup et al., 2017). In dengue virus infections, a phenomenon known as immunodomination can lead to biased T cell responses, where the immune system predominantly targets one serotype over others, potentially leading to suboptimal protection and increased disease severity upon subsequent infections with different serotypes (Lin et al., 2020). These examples underscore the complexity of the immune response to mosquito-borne pathogens and the challenges in balancing protective immunity with the risk of immunopathology.

The adaptive immune response to mosquito-borne pathogens involves intricate mechanisms of B cell activation and antibody production, as well as the critical roles of CD4+ and CD8+ T cells. However, the immune response can also lead to immunopathology, complicating the development of effective vaccines and therapies. Understanding these mechanisms and challenges is essential for advancing our ability to combat these diseases effectively (Torina et al., 2020; Raddi et al., 2020).

5 Immune Evasion Strategies Employed by Mosquito-Borne Pathogens

5.1 Antigenic variation and immune suppression mechanisms

Mosquito-borne pathogens have evolved sophisticated strategies to evade the host immune system, ensuring their survival and propagation. One of the primary mechanisms is antigenic variation, where pathogens alter their surface proteins to avoid detection by the host's immune system. For instance, Plasmodium falciparum, the causative agent of malaria, exhibits high antigenic variation through the expression of different surface antigens such as PfEMP1, which helps it evade immune responses and contributes to the chronicity of the infection (Jensen et al., 2019). Additionally, these pathogens can suppress the host immune response. P. falciparum, for example, can inhibit the activation of immune cells by expressing proteins like RIFIN that interact with inhibitory receptors on host cells, thereby dampening the immune response (Sakoguchi and Arase, 2022). Furthermore, the parasite can induce apoptosis in immune cells such as Kupffer cells and interfere with macrophage functions, which are crucial for the initial immune response (Belachew, 2018).

5.2 Case study: immune evasion in malaria-mechanisms employed by plasmodium

Plasmodium falciparum employs multiple strategies to evade the immune system of both its mosquito vector and human host. In the mosquito, the Pfs47 gene plays a critical role in evading the immune response by inhibiting the Janus kinase-mediated activation, which is essential for the mosquito's immune defense (Belachew, 2018). Additionally, the parasite recruits the human complement regulator Factor H to evade complement-mediated killing within the mosquito host (Schmidt et al., 2015). In the human host, P. falciparum utilizes antigenic variation and polymorphism to avoid immune detection. The parasite's ability to express different variants of surface proteins like PfEMP1 allows it to continuously evade the host's adaptive immune response (Jensen et al., 2019). Moreover, P. falciparum can suppress the host immune response by inducing apoptosis in Kupffer cells during the pre-erythrocytic stage and interfering with macrophage phagocytic functions during the erythrocytic

stage. The lack of major histocompatibility complex-I (MHC-I) molecule expression on the surface of infected red blood cells further prevents recognition by CD8+ T cells, allowing the parasite to survive and proliferate within the host.

6 Implications of Immune Responses for Vaccine Development and Therapeutics

6.1 Current progress in vaccine development for major mosquito-borne diseases

Recent advancements in vaccine development for mosquito-borne diseases have shown promising results. For instance, immunization with radiation-attenuated sporozoites (RAS) has demonstrated over 90% sterile protection against Plasmodium falciparum malaria in humans. Clinical trials have indicated that a higher initial dose followed by a reduced final dose can significantly enhance vaccine efficacy, achieving up to 90% protection in some cohorts (Hickey et al., 2020; Sedegah et al., 2021). Additionally, the development of a peptide-based vaccine derived from Anopheles gambiae salivary proteins has shown to be safe and immunogenic in humans, suggesting that vector-targeted vaccines could be a viable option for controlling mosquito-borne diseases (Manning et al., 2020).

6.2 Role of immunomodulators and biologics in enhancing protective immunity

Immunomodulators and biologics play a crucial role in enhancing protective immunity against mosquito-borne pathogens. Studies have shown that mosquito bites can modulate the immune response, leading to the recruitment of skin-resident dendritic cells and M2 macrophages, which are essential for initiating adaptive immune responses (Figure 3) (Guerrero et al., 2022; Cantaert et al., 2023). Furthermore, the use of adjuvants in vaccines, such as Montanide ISA 51, has been shown to significantly increase vaccine-specific IgG antibodies and IFN-γ production, thereby enhancing the overall immune response (Manning et al., 2020). These findings highlight the potential of using immunomodulators to boost vaccine efficacy and achieve long-lasting immunity.

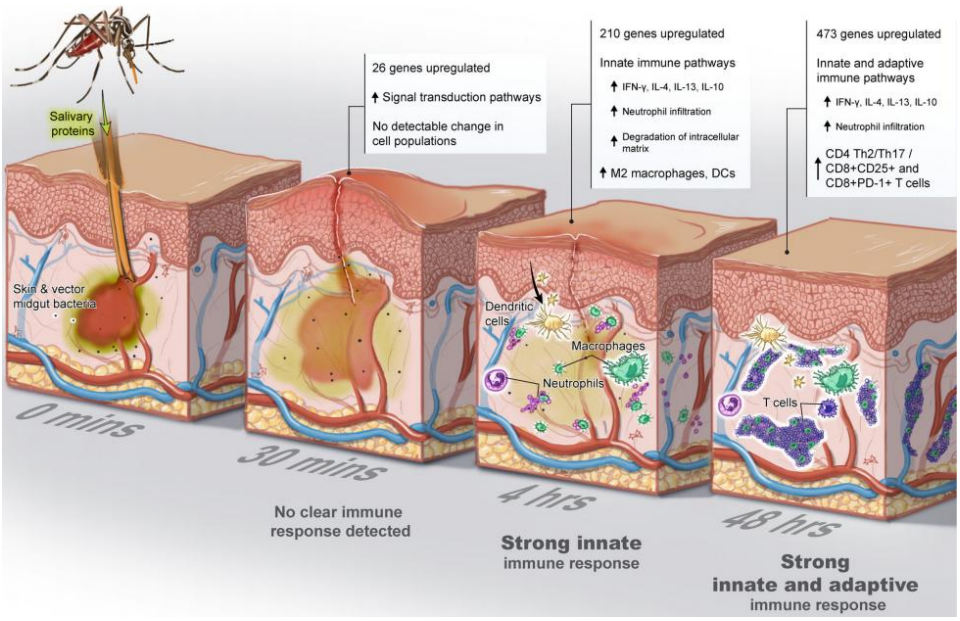

Figure 3 The cutaneous immune response to *Aedes aegypti* mosquito 'bites' evolves over time (Adopted from Guerrero et al., 2022)

Image caption: Little activity in gene regulation and cell populations were noted at 30 min. At 4 h post-bite, a clear innate immune signature emerged followed by a strong adaptive response at 48 h (Adopted from Guerrero et al., 2022)

7 Future Directions in Research

7.1 Integrating systems immunology approaches to study host-pathogen interactions

The integration of systems immunology approaches offers a comprehensive understanding of the complex interactions between host immune responses and mosquito-borne pathogens. Systems immunology combines omics technologies and computational sciences to analyze the immune response at a holistic level, moving beyond the reductionist view of studying individual genes or proteins in isolation. This approach can reveal dynamic

interactions and networks of cellular and molecular components that are crucial for developing effective interventions against diseases like malaria (Loiseau et al., 2020). For instance, recent studies have utilized systems-level approaches to investigate immune responses in the context of natural malaria exposure or controlled human malaria infection, providing valuable insights for the rational design of vaccines and therapeutics.

7.2 Emerging technologies in monitoring and modulating immune responses

Advancements in technology are revolutionizing the monitoring and modulation of immune responses to mosquito-borne pathogens. Techniques such as gene expression profiling, immunophenotyping, and cytokine profiling have been employed to assess the cutaneous immune response to mosquito bites, identifying key immune genes, cell types, and pathways involved in the human response (Cantaert et al., 2023). Additionally, intravital imaging has enabled real-time observation of immune cell recruitment to mosquito bite sites, offering insights into the immediate immune response to pathogens like Plasmodium (Rabinovich-Ernst et al., 2023). These technologies not only enhance our understanding of immune mechanisms but also pave the way for developing novel therapeutics and vector-targeted vaccines.

7.3 Prospective areas for interdisciplinary research

Interdisciplinary research is essential for addressing the multifaceted challenges posed by mosquito-borne diseases. One promising area is the study of the interactions between mosquito gut microbiota, the immune system, and pathogens. Understanding how microorganisms in the mosquito microbiota modulate immune responses and vector competence can inform the development of innovative control strategies, such as paratransgenesis or leveraging the relationship between Wolbachia and mosquito hosts (Gabrieli et al., 2021). Another critical area is the investigation of immune evasion mechanisms employed by pathogens like Plasmodium and flaviviruses, which can inform the design of effective vaccines and immunotherapies (Bhattacharjee et al., 2023; Chandley et al., 2023). Collaborative efforts across disciplines, including immunology, microbiology, and computational biology, are crucial for advancing our knowledge and developing comprehensive strategies to combat mosquito-borne diseases.

Future research in the field of human immune response to mosquito-borne pathogens should focus on integrating systems immunology approaches, leveraging emerging technologies for monitoring and modulating immune responses, and fostering interdisciplinary collaborations. These strategies will enhance our understanding of host-pathogen interactions, inform the development of novel therapeutics and vaccines, and ultimately contribute to the control and prevention of mosquito-borne diseases.

8 Concluding Remarks

The human immune response to mosquito-borne pathogens involves a complex interplay of innate and adaptive mechanisms initiated at the site of the mosquito bite. Mosquito bites trigger a cascade of immune responses, including neutrophil degranulation, recruitment of skin-resident dendritic cells, and activation of T cells, which are crucial in shaping the establishment of infection and subsequent pathogenesis. For instance, the recognition of Plasmodium sporozoites at the bite site involves rapid recruitment of immune cells and specific gene expression patterns, although the parasite can modulate these responses to evade immunity. Additionally, mosquito-borne pathogens employ immune evasion strategies, such as interfering with antigen presentation and modulating T cell activation, which are pivotal in understanding disease progression and the potential stimulation of non-communicable diseases. In flavivirus infections like dengue and Zika, the interferon system and antibody-mediated responses highlight the dual role of the immune system in both protection and pathogenesis. Furthermore, immune responses in mosquitoes, including the activation of antimicrobial peptides and reactive oxygen species, significantly influence pathogen propagation and represent potential targets for disease control strategies.

To effectively leverage immune response research in managing mosquito-borne diseases, several strategies can be recommended. The development of targeted vaccines and therapeutics is a critical approach, as understanding the

specific immune pathways activated by mosquito bites and pathogen infections can inform innovative solutions. For example, targeting key immune genes and pathways identified in human responses to mosquito bites can lead to the creation of vector-targeted vaccine candidates. Additionally, insights into the mosquito's innate immune responses, such as the role of antimicrobial peptides and reactive oxygen species, offer opportunities to develop new vector control methods. Manipulating the expression of specific immune-related genes in mosquitoes could significantly reduce their capacity to transmit pathogens.

Improving diagnostic tools and promoting integrated disease management further strengthen these efforts. The dual role of the immune system in protection and pathogenesis, particularly in flavivirus infections, underscores the need for advanced diagnostic tools that can differentiate between protective and pathogenic immune responses, aiding in better disease management and treatment strategies. Integrating immune response research with traditional vector control measures and public health initiatives can provide a more comprehensive approach to managing mosquito-borne diseases. This includes community education, environmental management, and utilizing immunological insights to predict and prevent outbreaks. In summary, leveraging a detailed understanding of immune responses to mosquito-borne pathogens can significantly enhance prevention, diagnosis, and treatment strategies for these globally significant diseases.

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Conflict of Interest Disclosure

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