



# Recent Advances in Host–Pathogen Interactions and Innate Immune Responses in Mosquitoes: Emerging Molecular Mechanisms and Novel Vector Control Strategies

**Jeyasankar A\***

Department of Zoology, Government Arts College (Autonomous), India

**\*Corresponding author:** Jeyasankar Alagarmalai, Department of Zoology, Government Arts College (Autonomous), India

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## Abstract

Mosquitoes are the principal vectors of malaria parasites, arboviruses, and filarial nematodes, causing significant morbidity and mortality. Recent advances in molecular immunology have revealed that mosquitoes possess a highly sophisticated innate immune system that regulates pathogen establishment, replication, and transmission in the host. In addition to the classical Toll, IMD, JAK–STAT, RNA interference (RNAi), and melanization pathways, emerging studies have identified crucial roles for microbiome-mediated immunity, immunometabolism, epigenetic regulation, non-coding RNAs, and genome engineering in determining vector competence. Single-cell transcriptomics, spatial omics, CRISPR/Cas9 technology, and artificial intelligence-based systems biology have further revolutionized our understanding of mosquito–pathogen interactions.

**Keywords:** Vectors; Immune; Microbiome; Genome Engineering; Malaria; Arboviruses

## Introduction

Mosquito-borne diseases continue to threaten nearly half of the global population despite extensive vector control programs (WHO, 2024). Traditionally, mosquitoes have been regarded as passive carriers of pathogens; however, recent evidence indicates that mosquito vectors actively regulate pathogen survival through complex innate immune mechanisms [1]. Modern mosquito immunology deals with

vector competence genes, immune signaling networks, microbiome-host interactions, immunometabolism, epigenetic regulation, and genome engineering, which have transformed mosquito biology from descriptive entomology into a multidisciplinary field that integrates molecular genetics, immunology, microbiology, and computational biology [2].

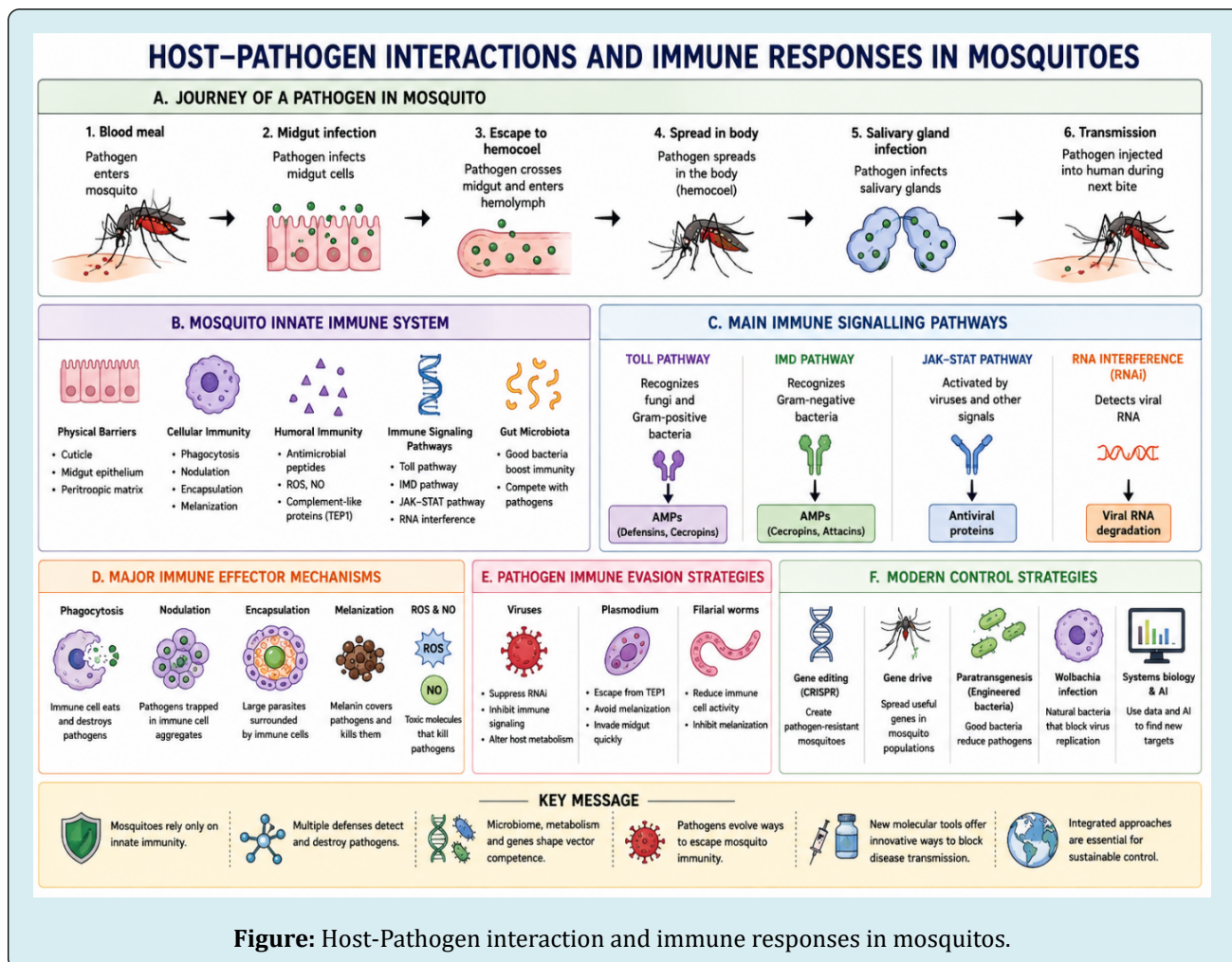


**Figure:** Host-Pathogen interaction and immune responses in mosquitos.

### Vector Competence: A Multifactorial Trait

Vector competence is now recognized as a quantitative phenotype regulated by interactions among mosquito genetics, pathogen genotypes, environmental factors, nutrition, microbiota, and immune responses [3]. Recent genome-wide association studies (GWAS) have demonstrated that hundreds of mosquito genes collectively influence susceptibility to the dengue virus, *Plasmodium falciparum*, and the West Nile virus, rather than a few major resistance loci [4]. The importance of the midgut, hemocoel, and salivary gland barriers collectively determines whether a pathogen successfully completes its extrinsic incubation period [5].

### Pattern Recognition Receptors: The First Line of Defence

Mosquito innate immunity begins with pathogen recognition through pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) [6]. The major receptor families include Peptidoglycan

Recognition Proteins (PGRPs), Gram-negative Binding Proteins (GNBPs), C-type Lectins, Galectins, Scavenger Receptors, Thioester-containing proteins (TEPs), and fibrinogen-related proteins (FREPs). Among these, TEP1 functions similarly to vertebrate complement C3 and remains one of the strongest natural transmission-blocking molecules against *Plasmodium* spp. [7]. Recent proteomic analyses have indicated that PRRs form dynamic receptor complexes that enhance pathogen specificity and amplify immune responses [6].

### Immunometabolism: Linking Homeostasis with Immunity

Immunometabolism is one of the most rapidly expanding areas in mosquito research. Pathogen infection induces profound metabolic reprogramming, including glycolysis, oxidative phosphorylation, lipid metabolism, and amino acid biosynthesis [2]. Dengue virus actively manipulates host lipid metabolism to facilitate virion assembly, whereas *Plasmodium* infection alters mitochondrial respiration and redox balance to evade oxidative stress [1]. Metabolomic

profiling suggests that enzymes involved in fatty acid synthesis and mitochondrial metabolism may serve as promising transmission-blocking targets [5].

### Single-Cell and Spatial Omics

Single-cell RNA sequencing (scRNA-seq) has transformed mosquito immunology by revealing cellular heterogeneity that was previously masked by bulk transcriptomic analysis. Recent investigations have identified novel granulocyte subsets, antiviral hemocyte populations, tissue-specific immune signatures, infection-induced cellular differentiation, and specialized immune functions within the fat body of insects. Spatial transcriptomics has further demonstrated that immune responses differ markedly between the midgut, hemocoel, ovaries, and salivary glands, highlighting tissue-specific regulation of vector competence [8].

### Epigenetic Regulation of Mosquito Immunity

Recent evidence indicates that mosquito immune responses are strongly influenced by epigenetic modifications, including DNA methylation, histone acetylation, histone methylation, RNA methylation (m6A), and chromatin remodeling [9]. Non-coding RNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), PIWI-interacting RNAs (piRNAs), and circular RNAs (circRNAs), modulate immune gene expression and antiviral responses [10]. Notably, *Wolbachia* infection alters m6A methyltransferase activity, thereby enhancing antiviral immunity against dengue virus [11].

### Microbiome-Driven Immunity

The mosquito gut microbiome is increasingly recognized as an essential component of innate immunity and beneficial bacteria of *Wolbachia*, *Asaia*, *Enterobacter*, and *Serratia*, which enhance basal immune activation by stimulating Toll and IMD signaling pathways while competing directly with pathogens for nutrients and epithelial binding sites [12]. *Wolbachia*-infected mosquitoes exhibit reduced replication of dengue, Zika, chikungunya, and yellow fever viruses through immune priming and metabolic competition [11]. These findings have accelerated the development of microbiome engineering and paratransgenesis as sustainable alternatives to conventional insecticides [1].

### Immune Evasion by Mosquito-Borne Pathogens

Successful pathogens have evolved multiple mechanisms to evade mosquito immunity. Recent studies have demonstrated that arboviruses suppress RNA interference by producing viral suppressor proteins, inhibiting JAK-STAT signaling, altering host lipid metabolism, and interfering

with apoptosis [2]. Similarly, *Plasmodium* ookinetes evade complement-like TEP1-mediated killing through surface protein polymorphisms and rapid epithelial invasion [7]. These sophisticated immune evasion strategies substantially contribute to the vector competence.

### Genome Editing and Future Vector Control

CRISPR/Cas9 technology has transformed mosquito functional genomics. Current applications include the knockout of immune regulatory genes, enhancement of antimicrobial peptide production, engineering of pathogen-resistant mosquitoes, validation of vector competence genes, and gene drive development. Gene drives capable of spreading pathogen-resistant alleles through mosquito populations represent one of the most promising long-term strategies for disease elimination, although ecological and ethical considerations remain to be investigated [13].

### Artificial Intelligence and Multi-Omics Integration

Artificial intelligence has become increasingly valuable for integrating transcriptomic, proteomic, metabolomic, microbiomic, and genomic data. Machine learning algorithms can identify candidate immune regulators, predict vector competence, and prioritize transmission-blocking targets for experimental validation [8]. The integration of systems biology with AI is expected to transform mosquito immunology into a predictive science that can anticipate the emergence of vector-borne diseases.

### Conclusion

Mosquito innate immunity is considerably more complex than previously recognized. Contemporary research has demonstrated that vector competence results from interactions among immune signaling pathways, the microbiota, metabolism, epigenetic regulation, and environmental factors. Emerging technologies, including single-cell transcriptomics, CRISPR/Cas9 genome editing, microbiome engineering, and AI-assisted systems biology, are reshaping our understanding of mosquito-pathogen interactions and providing innovative avenues for transmission-blocking strategies. The continued integration of molecular biology, computational science, and vector ecology is essential for developing sustainable strategies to control mosquito-borne diseases.

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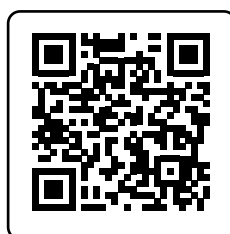
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