Mutation of Dengue Virus Envelope Protein and Mechanism of Cross-Host Transmission

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Abstract. Dengue virus spreads worldwide. Mosquitoes of the Aedes genus pass it to humans. The virus poses big risks to global public health. Its envelope protein, E protein, controls three key viral behaviors. It lets viruses recognize host cells, fuse cell membranes and live through changing environments. Most adaptive non-synonymous mutations appear on the gene that makes E protein. These amino acid changes reshape the protein's 3D structure. This change lets dengue jump across different host species. This paper sorts out E protein structures and sites where mutations often happen. It explains how single amino acid changes affect virus heat resistance, receptor binding speed and intracellular replication. Mutated E proteins help viruses escape mosquito immune defenses. They also help viruses survive stress inside mammalian cells. This paper builds a full molecular path to explain how dengue shifts between mosquitoes and people. Current research has clear limits. Few studies measure how multiple mutations work together. Lab cell models cannot copy real infection environments. Long-term tracking of wild virus strains is rare. This work improves theories about dengue's evolution in two hosts. It picks out key adaptive mutation sites. It offers theory support for epidemic early warning, broad-spectrum vaccine design and new antiviral drug research.

Keywords: Dengue virus, envelope protein, amino acid mutation, cross-host transmission, adaptive evolution.

1. Introduction

Dengue fever is one of the most common mosquito-borne viral diseases. It hits tropical and subtropical areas all over the world. The WHO released its 2025 surveillance report. It counts nearly 390 million dengue infections every year globally. Around 96 million infected people show obvious clinical symptoms [1]. Aedes albopictus and Aedes aegypti spread this virus. They bring lasting threats to public health worldwide. Global warming and frequent cross-border travel widen dengue's spread range. Areas with little past dengue risk now face repeated outbreaks.

Dengue mutates far faster than many other viruses. Frequent gene changes help it survive different environments and hosts. This trait explains its strong transmission ability. E protein is the main surface structural protein of dengue virus. It handles host recognition, cell attachment and membrane fusion [2]. Existing studies confirm most adaptive mutations sit on the E protein gene [3]. Small amino acid shifts alter the protein's spatial shape and change viral infectivity. Four dengue serotypes all carry frequent mutation hotspots on E protein. These variant sites link to different disease levels. Cases range from mild fever to deadly dengue shock syndrome. Commercial dengue vaccines fail to protect people against all serotypes. Most antiviral drugs targeting E protein domains only stay in preclinical trials.

Most past papers only discuss E protein mutation, virus virulence and disease severity. Few studies systematically explain how these mutations break species barriers. Researchers have not fully organized the full molecular chain of cross-host transmission between mosquitoes and humans.

This paper fills the above research gaps. It focuses on mutation features of dengue E protein. It analyzes how key variant sites change virus structural stability and host receptor binding ability. It further explores molecular paths through which E protein mutations drive viral evolution and transmission from mosquitoes to humans.

This study holds both theoretical and practical value. In theory, it supplements research on dengue adaptive evolution and cross-host infection mechanisms [4]. It builds a more complete framework to

interpret dengue genetic variation. In practice, this paper marks core mutation sites linked to cross-host adaptation. These markers support routine dengue monitoring, early detection of new variants, and targeted vaccine and drug development

2. Overview of Dengue Virus and Envelope Protein

2.1. Basic Biological Characteristics of Dengue Virus

Dengue virus belongs to Flavivirus, Flaviviridae family. It is an enveloped positive single-stranded RNA arbovirus [5]. Its genome is about 11 kilobases long. It encodes one long polyprotein precursor. Viral and host enzymes cut this precursor into structural and non-structural proteins. Three structural proteins form after cleavage: C capsid protein, prM membrane protein and E envelope protein. Seven non-structural proteins control replication, immune escape and virus assembly. Four serotypes circulate globally: DENV-1, DENV-2, DENV-3, DENV-4. Immunity from one serotype cannot block infection from other types. Secondary infection with a different serotype raises antibody-dependent enhancement (ADE) risk sharply. ADE causes dengue hemorrhagic fever and fatal shock syndrome [6]. Dengue is a typical dual-host arbovirus. It cycles between female Aedes mosquitoes and human hosts. When mosquitoes take blood meals, viruses first invade midgut epithelial cells. They then move to salivary glands for transmission via bites. Inside human bodies, viruses mainly infect dendritic cells, monocytes and macrophages to replicate in large numbers. The virus lives in cold-blooded insects and warm human bodies alternately. This creates constant selection pressure on its genome. It keeps high genetic flexibility and enables frequent adaptive mutations [7].

2.2. Structural CComposition and Biological Functions of E Protein

E protein is the most abundant protein on dengue virus lipid shells. It forms antiparallel homodimers under neutral extracellular pH. Scientists split it into three independent functional domains with separate jobs. Domain I forms the rigid central backbone of the protein. Domain II extends outward and controls membrane fusion. Domain III folds like immunoglobulin. It identifies and binds host cell receptors [8]. Host cells wrap viruses into endosomes after absorption. Acidic pH inside endosomes changes E protein dimer shapes irreversibly. Dimers split and recombine into stable trimers. This move exposes hidden hydrophobic fusion peptides inside Domain II. Exposed fusion segments insert into endosome lipid membranes. They pull viral and host membranes together to finish fusion. Viral RNA releases into cell cytoplasm to start replication [9]. Besides cell invasion, E protein carries major neutralizing epitopes. These epitopes are the main targets of human antibody responses. They also serve as core targets for vaccine and antiviral drug development.

2.3. Key Mutation Sites of dengue E Protein

Global whole-genome sequencing data of epidemic strains shows adaptive non-synonymous mutations gather heavily on E protein coding sequences. Two high-frequency mutation zones lie on Domain II and Domain III [10]. Domain II hotspot mutations cluster around fusion peptides and dimer contact surfaces. Amino acid substitutions here change force balance between paired E proteins. They shift the critical pH value needed for structural rearrangement and membrane fusion. Domain III mutation hotspots sit on outer loops for receptor binding. Variants here reshape the geometry of receptor binding pockets. They change binding strength between viruses and host receptors such as heparan sulfate, DC-SIGN and mannose receptors. Domain I stays highly conserved with rare mutations. Most amino acid changes here break the whole protein backbone and kill viral activity. Natural selection eliminates these defective strains during evolution.

3. Relationship between E Protein Mutation and Viral Adaptability

3.1. Effect of E Protein Mutation on Viral Structural Stability

Multiple forces maintain E protein spatial shape. These forces include intramolecular hydrogen bonds, hydrophobic stacking, electrostatic attraction and fixed disulfide bond pairs. Single missense amino acid mutations break the original force balance inside protein molecules. They alter overall structural hardness and environmental resistance of intact viruses. Some adaptive amino acid substitutions strengthen hydrophobic core stacking inside E protein. This improvement lets viruses better resist temperature rises, osmotic changes and protease breakdown outside cells. Stronger structural stability lengthens virus survival time in natural environments. It raises the chance of successful transmission between different hosts. By contrast, random harmful mutations break conserved disulfide bonds and internal hydrogen bond networks. They make parts of the protein unfold. Viruses with these damaging mutations assemble poorly. They release fewer particles outside cells and cannot stand environmental stress. Natural selection gradually removes these strains from epidemic populations. Only mutations that stabilize protein structures pass down steadily. They build up in dominant epidemic strains after multiple transmission cycles.

3.2. Influence of Mutation on Virus Binding to Host Receptors

E protein Domain III holds core receptor-binding regions. Amino acid substitutions here directly change how fast viruses attach to host cell receptors. Mutations that add positively charged amino acids strengthen electrostatic attraction. Heparan sulfate with negative charge spreads widely on mammalian cell surfaces. This change speeds up initial virus attachment and improves infectivity toward human cells [11]. Some adaptive mutations widen the range of host receptors the virus can recognize. Mutated E proteins bind new membrane protein receptors ignored by wild-type strains. This expands the types of cells the virus can infect. It widens dengue's host adaptation range. Such receptor preference shifts are one core molecular way flaviviruses break species barriers.

3.3. Correlation between Mutation and Viral Replication Efficiency

E protein mutations adjust intracellular virus replication speed through multiple linked pathways. Viruses with stabilized mutated E proteins escape lysosomal degradation and host autophagy after entering cells. Complete viral genetic material can start replication smoothly [12]. Strains with stabilizing E protein mutations keep high replication levels in monocytes and macrophages. They produce large numbers of new viruses within short incubation periods. E protein variants also indirectly block host innate immune signal transmission. Viruses that enter cytoplasm via optimized E protein fusion delay interferon antiviral pathway activation. This creates an immune-suppressed cell environment. The environment supports continuous viral genome replication and new virus assembly. More replicated viruses provide sources for secondary infection and cross-host spread.

4. Molecular Mechanism of Cross-host Transmission Caused by E Protein Mutation

4.1. Adaptive Mechanism of Virus Infecting Mosquito Vectors

Mosquitoes ingest dengue virus when they feed on blood. Viruses must cross two key barriers: midgut infection barrier and salivary gland escape barrier. Adaptive E protein mutations help viruses evade two major mosquito defense systems. These systems are RNAi antiviral pathways and Toll innate immune responses [13]. Modified E proteins lower mosquito immune receptors' ability to recognize foreign viruses. They cut down downstream antiviral factor production. Viruses can replicate steadily inside insect cells. E protein mutations adjust virus membrane fusion efficiency to match low-temperature environments inside mosquitoes. Fusion activity fits acidic endosome conditions unique to insect cells. Well-adapted viruses cross midgut epithelial layers and move to

salivary glands. Mature viruses build up in gland tissue. Mosquitoes carry viruses permanently and gain transmission ability to humans.

4.2. Molecular Casis of Virus Cross-Infecting Mammalian Hosts

Big temperature differences between insects and human bodies create heavy physiological pressure for cross-species transmission. Human bodies stay at nearly 37℃. This temperature speeds up protein thermal denaturation. E proteins need adaptive amino acid mutations to gain stronger thermal stability [14]. Adaptive substitutions on E protein domains lift the temperature threshold for protein denaturation. They stop premature structural breakdown under human body temperature before cell invasion. Mammalian cell endosomes acidify at different speeds than insect cell organelles. Key E protein mutations reset pH sensitivity for structural shifts. They match membrane fusion speed to human intracellular acidic environments. Without these adaptive changes, viral envelopes cannot fuse with mammalian cell membranes. Viruses fail to release genetic material to trigger infection.

4.3. Key Mutation Sites Driving Cross-Host Transmission

Long-term epidemiological tracking and reverse genetic site mutation tests confirm several fixed E protein variant loci. These sites closely link to mosquito-human cross-species transmission [15]. These amino acid mutation sites carry dual adaptive features. They meet structural and functional needs inside cool mosquito bodies and thermally stable human bodies. They act as core molecular markers to track dengue cross-host evolution. Continuous monitoring of these transmission-related mutation hotspots tracks evolutionary trends of dominant epidemic strains. Researchers judge possible host range expansion risks. They collect molecular evidence to trace cross-region dengue outbreak spread paths.

5. Problems and Challenges in Current Research

5.1. Unclear Mutation Superposition Effect

Most existing research uses site-directed mutagenesis to study single-site point mutations of dengue E protein. It observes related phenotypic changes. But wild circulating dengue strains usually carry multiple amino acid mutation sites at the same time [16]. Interactions between different variant sites include synergistic enhancement and antagonistic offset effects. Researchers lack systematic quantitative research and deep mechanism explanation for these interactions. Unclear combined mutation effects stop full understanding of dengue's overall evolution rules for host adaptation and transmission changes.

5.2. Limitations of cross-Host Transmission Simulation Experiments

Most current lab studies use separate mammalian or mosquito cell lines for in vitro infection tests. These tests observe infectivity changes brought by E protein mutations. Simplified single-layer cell culture models cannot copy complex full physiological environments inside whole mosquitoes and multi-organ human tissues [17]. Data from isolated cell systems shows clear gaps with real in vivo cross-host transmission processes. It reduces practical reference value for actual epidemic situations. Whole-animal infection verification experiments remain rare. High experimental costs and strict biosafety limits restrict such tests.

5.3. Deficiencies in Mutation Monitoring and Early Warning

Next-generation high-throughput gene sequencing sees wide use now. Even so, large-scale real-time dynamic monitoring of wild dengue strain mutations faces many bottlenecks. Testing costs stay high, and data analysis workflows remain complex [18]. Specialized early warning platforms targeting E protein cross-host adaptive mutation hotspots have not matured into usable tools. Current monitoring mostly runs retrospective gene sequence analysis after dengue outbreaks happen. The field cannot predict sudden outbreak risks from newly emerged adaptive mutant strains.

6. Conclusion

This paper reviews basic biological traits of dengue virus and structural functions of E protein. It sorts out inner connections between E protein mutation and viral host adaptability. Mutation hotspots of E protein mainly lie on Domain II and Domain III. Domain I keeps high conservation due to strict structural limits.

Adaptive amino acid substitutions balance intramolecular forces inside E protein. They improve virus heat resistance and environmental tolerance. They reshape receptor binding pockets to expand recognizable host cell receptor types. Mutated E proteins help viruses escape lysosomal autophagy breakdown. They slow human interferon immune responses and greatly raise intracellular replication levels.

When discussing cross-host transmission mechanisms, E protein mutations give dengue dual adaptive capacity. Inside mosquito vectors, variant E proteins suppress RNAi and Toll immune pathways. Viruses break midgut and salivary gland infection barriers. Inside human mammalian hosts, stabilizing mutations raise E protein thermal unfolding thresholds. They adjust pH-dependent structural rearrangement speed to fit human constant-temperature cell environments. Specific dual-adaptive mutation loci mark viral cross-species spillover events.

Current research has obvious defects. Researchers cannot quantify synergistic and antagonistic effects of multiple overlapping mutations. Simplified monolayer cell models fail to copy full vector and mammalian physiological environments. Experimental data differs from real transmission rules. High testing costs and complex analysis limit large-scale dynamic monitoring of wild mutant strains. No mature early warning systems target cross-host adaptive mutations for daily use.

Future basic research can use reverse genetic manipulation based on infectious clones. It quantifies interactions between multiple E protein mutation sites. It reveals overall evolution rules of compound mutations regulating viral host adaptability. Teams should carry out more whole-animal in vivo infection verification tests. These tests remove bias from in vitro cell models and restore real dynamic cross-host transmission processes. Combined with high-throughput NGS sequencing, long-term epidemiological tracking of cross-host mutation hotspots predicts host range expansion risks of epidemic strains.

For real public health use, core adaptive mutation loci summarized in this paper work as monitoring markers for routine dengue virus surveillance. These markers support prediction early warning platforms for variant-caused outbreaks. Conserved E protein functional domains and mutated epitopes become core design targets for broad-spectrum cross-serotype vaccines and small-molecule antiviral drugs. These targets fix cross-protection defects of existing commercial vaccines. They speed up preclinical research of targeted anti-dengue compounds. Long-term study of E protein-mediated cross-host adaptation mechanisms builds solid theoretical foundations for global dengue prevention and control.

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