## 4 The Key Mechanisms of the Severe Dengue Fever Immune Storm

### 4.1 Overactivation of innate immunity and pattern recognition receptor pathways

Innate immunity is the first line of defense of the human body against the dengue virus (DENV). Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), are responsible for recognizing the virus and initiating an inflammatory response. After DENV infection, TLR2, TLR4 and TLR6 in immune cells are often activated, leading to an increase in pro-inflammatory factors such as IL-6 and TNF-α. Among them, the NS1 protein of DENV can activate TLR2, TLR4 and TLR6, directly promoting immune cells to release cytokines, intensifying immune storm and tissue damage (Fernandez-santos and Azeredo, 2022). The strong response of innate immunity can initially fight viruses, but if it goes too far, it will get out of control. Excessive TLR signals will increase vascular permeability, which is an important feature of severe dengue fever.

Plasma leakage often occurs after a decrease in viral load, suggesting that severe manifestations are more due to uncontrolled host immunity rather than direct cell destruction by the virus (Fernandez-Santos and Azeredo, 2022). If pattern recognition receptors (PRRs) are overly or abnormally activated, they will rapidly trigger a series of inflammatory responses, which is precisely the basis for the formation of an immune storm.

### 4.2 Antibody-dependent enhancement and abnormal T-cell response

Antibody-dependent enhancement (ADE) is regarded as one of the important reasons for the aggravation of dengue fever, especially when reinfected with different serotypes of viruses. During the ADE process, antibodies that cannot neutralize the virus will "bring" the virus into immune cells expressing Fcγ receptors (such as monocytes), thereby increasing the replication level of the virus in the body and inducing overactivation of the immune system (Figure 1) (Sun et al., 2025). Subsequently, a large number of inflammation-related cytokines are released, further promoting the development of the immune storm, which can eventually lead to vascular leakage and shock (Shabbir and Linh, 2024).

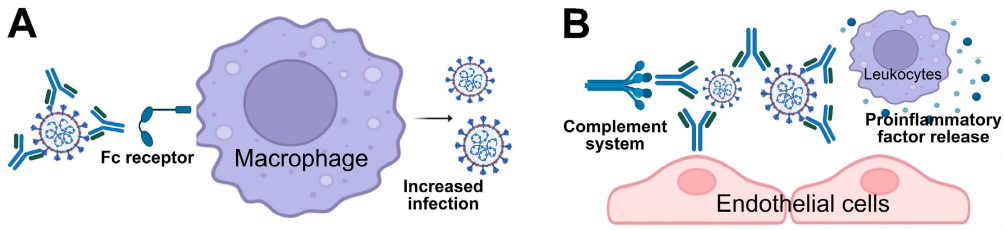


Figure 1 Two proposed mechanisms of ADE in viral disease exacerbation (Adopted from Sun et al., 2025)

Image caption: This figure illustrates two potential mechanisms of ADE contributing to viral disease pathogenesis, as suggested by previous studies; (A) In ADE via increased infection, non-neutralizing or sub-neutralizing antibodies enhance the viral infection of macrophages or other Fc-receptor-bearing cells through Fc-receptor-mediated endocytosis. This process leads to increased viral replication and a more severe disease phenotype; (B) In ADE via enhanced immune activation, non-neutralizing antibodies form immune complexes with viral antigens within tissues such as blood vessels or airways. These immune complexes trigger the release of proinflammatory cytokines, the recruitment of immune cells, and the activation of the complement cascade, resulting in localized tissue damage and inflammation (Adopted from Sun et al., 2025)

Abnormal T cell function also increases the risk of severe illness. Some memory T cells formed by previous infections can "recognize" different serotypes of viruses, but their response to secondary infections is often inefficient - these cells tend to release pro-inflammatory factors but have difficulty effectively eliminating the virus. This phenomenon is known as "original antigen imprinting". When the ADE effect superimposed with this abnormal T-cell response, it would promote an increase in viral load and aggravation of inflammation, forming a vicious cycle (Shabbir and Linh, 2024).

### 4.3 Vascular endothelial injury leading to complement and coagulation abnormalities and vascular stability disruption

Vascular endothelial injury is an important pathological feature of severe dengue fever. After entering endothelial cells, the dengue virus triggers an inflammatory response, increases the expression of various chemokines, promotes the aggregation of immune cells, and causes significant cellular damage during the disease's progression.