Japanese encephalitis virus NS3 captures the protein translation element by interacting with HNRNPH1 to promote viral replication

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Background: Japanese encephalitis virus (JEV), a neurotropic flavivirus, is a leading cause of viral encephalitis in Asia and is associated with severe neurological complications in both humans and animals. While aspects of its pathogenesis have been characterized, the mechanism by which JEV exploits the host translational machinery to support its replication remain poorly understood. Heterogeneous nuclear ribonucleoprotein H1 (HNRNPH1), an RNA binding protein involved in mRNA processing, has emerged as a potential host factor influencing viral replication. However, its specific role during JEV infection has yet to be fully elucidated.

Objective: This study aims to investigate the role of HNRNPH1 in JEV replication and its regulation by the transcription factor SOX10.

Results: HNRNPH1 was significantly downregulated at both mRNA and protein levels in JEV-infected HEK293T cells in a time- and dose-dependent manner. Co-immunoprecipitation and GST pull-down assays demonstrated a direct, RNA-independent interaction between HNRNPH1 and JEV NS3 protein. Confocal microscopy confirmed their cytoplasmic co-localization during JEV infection. Overexpression of HNRNPH1 enhanced JEV replication, while siRNA-mediated knockdown suppressed viral RNA levels, protein expression, and infectious titers. Promoter truncation and luciferase assays revealed a core promoter region (−30 to +1) driving HNRNPH1 transcription. Among candidate transcription factors, only SOX10 overexpression restored HNRNPH1 expression and promoter activity; conversely, SOX10 knockdown reduced them. HNRNPH1 silencing activated antiviral signaling by upregulating MDA5 and RIG-I expression and enhancing IFN-β promoter activity, whereas its overexpression suppressed these responses. Additionally, HNRNPH1 physically interacted with PABPC1, eIF4E, and eIF4A independent of RNA. Co-expression of HNRNPH1 and NS3 facilitated recruitment of host translation machinery and promoted viral mRNA translation.

Conclusion: HNRNPH1 interacts with NS3 to recruit host translation machinery and suppresses antiviral signaling, while its expression is transcriptionally downregulated by JEV through SOX10 inhibition. These findings offer new insights into JEV pathogenesis and suggest potential targets for antiviral intervention.