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Nuclear Components Interacted with Dengue Virus Core Protein and Their Role in Virus Replication and Pathogenesis

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ABSTRACT
In this study, we investigated the interactions between the dengue virus (DENV) core protein and various nuclear components, examining their significance in virus replication and pathogenesis. Key findings revealed that the DENV core protein interacted with nucleolin, facilitating its transport to the nucleolus and enhancing viral RNA replication. Histone H1 binding by the DENV core protein promoted chromatin remodeling necessary for efficient viral replication, while its interaction with poly(A)-binding protein nuclear 1 (PABPN1) stabilized viral RNA in the nucleus. Furthermore, association with splicing factor SFPQ modulated alternative splicing of host pre-mRNAs, optimizing viral replication. Nuclear factor 90 (NF90) and NF-κB signaling were also activated, promoting viral replication and contributing to immune evasion. Finally, interactions with nucleophosmin (B23) and SUMO proteins supported viral replication by affecting host protein localization and function. These interactions played a pivotal role in altering host cell processes, leading to apoptosis, inflammation, and immune evasion, ultimately contributing to the pathogenesis of dengue infection.
Keywords: Dengue virus, DENV core protein, virus replication, nucleolin, histone H1, PABPN1, SFPQ, NF90, NF-κB, nucleophosmin, SUMO, pathogenesis

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INTRODUCTION

The Dengue virus (DENV) core protein plays a pivotal role in virus replication and pathogenesis through its interactions with various nuclear components of the host cell. These interactions are critical for enhancing viral replication and contributing to the pathophysiological effects observed during infection. The DENV core protein, a small structural protein, is primarily involved in packaging the viral genome, but recent studies have highlighted its multifaceted role in manipulating host cellular functions to favor viral replication and immune evasion.

Research on the DENV core protein has demonstrated that it interacts with nucleolin, a multifunctional protein found in the nucleolus. This interaction facilitated the transport of the core protein to the nucleolus, which was essential for enhancing viral RNA replication. Additionally, the interaction with nucleolin altered host cell functions, contributing to DENV-induced pathogenesis (Balinsky et al., 2013). Another nuclear component, histone H1, which regulates chromatin structure, was shown to bind to the DENV core protein. This interaction promoted chromatin remodeling, necessary for efficient viral replication, and led to changes in host gene expression that affected cell survival and immune responses (El-Bacha et al., 2007). The DENV core protein also formed complexes with poly(A)-binding protein nuclear 1 (PABPN1), stabilizing viral RNA within the nucleus and aiding in viral genome replication. This interaction disrupted normal RNA processing and transport, which contributed to disease symptoms (Ward et al., 2011). Furthermore, the association of the DENV core protein with the splicing factor SFPQ modulated the alternative splicing of host pre-mRNAs, optimizing the cellular environment for viral replication and interfering with host cellular functions, ultimately leading to apoptosis and inflammation (Zhang et al., 2018).

Interactions between the DENV core protein and nuclear factor 90 (NF90) were found to enhance the stability and translation of viral RNA, affecting host antiviral responses and contributing to immune evasion (Ismail et al., 2004). Similarly, the activation of NF-κB signaling pathways by the DENV core protein promoted viral replication by upregulating genes involved in viral genome synthesis. This activation also induced inflammatory responses, leading to severe disease manifestations, including

hemorrhagic fever (Sreekanth et al., 2016). Moreover, the DENV core protein co-localized with nucleophosmin (NPM1/B23), supporting the assembly of viral replication complexes and causing redistribution of NPM1, which disrupted normal cellular processes (Tseng et al., 2016). Additionally, the DENV core protein was modified by SUMO proteins through SUMOylation, a post-translational modification that influenced the localization and function of viral proteins, enhancing replication. This modification also altered host protein functions, contributing to immune modulation and pathogenesis (Chang et al., 2011).

These findings underscore the importance of nuclear interactions in the life cycle of DENV and their implications for viral pathogenesis, emphasizing the potential of these interactions as targets for antiviral strategies.

MATERIAL AND METHODS

Study Design and Sample Collection

This study was conducted to investigate the interactions between the Dengue virus (DENV) core protein and specific nuclear components, as well as their significance in viral replication and pathogenesis. In vitro experiments were designed to mimic the conditions of viral infection in human host cells. Human hepatocellular carcinoma cells (Huh-7), a well-established cell line for studying DENV infection, were used for this research. The cells were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin, and 1% L-glutamine. The DENV serotype 2 (DENV-2) strain was used to infect the cells.

Viral Infection Protocol

Huh-7 cells were seeded in 6-well plates and incubated overnight at 37°C in a 5% CO_2 atmosphere. The next day, the cells were infected with DENV-2 at a multiplicity of infection (MOI) of 1.0. After 2 hours of viral adsorption, the infection medium was replaced with fresh DMEM supplemented with 2% FBS. The cells were then incubated for different time points (24, 48, and 72 hours post-infection) to allow for the analysis of viral replication and protein interaction dynamics. Mock-infected cells were maintained as controls for each time point.

Protein Extraction and Immunoprecipitation

Total cellular proteins were extracted from both infected and mock-infected cells using radioimmunoprecipitation assay (RIPA) buffer supplemented with protease inhibitors. The lysates were clarified by centrifugation at 12,000 g for 15 minutes at 4°C. Immunoprecipitation was performed using protein-specific antibodies targeting nucleolin, histone H1, poly(A)-binding protein nuclear 1 (PABPN1), splicing factor proline and glutamine-rich (SFPQ), nuclear factor 90 (NF90), nuclear factor kappa light chain enhancer of activated B cells (NF-κB), nucleophosmin, and small ubiquitin-like modifier (SUMO) proteins. The DENV core protein was immunoprecipitated using a monoclonal anti-DENV core antibody. Protein complexes were isolated by incubating the lysates with the corresponding antibodies and protein A/G agarose beads overnight at 4°C. The beads were washed three times with RIPA buffer, and the bound proteins were eluted using Laemmli sample buffer.

Western Blotting

Western blotting was performed to confirm the interaction between the DENV core protein and the nuclear components. The protein samples were separated by **SDS-PAGE** and transferred to nitrocellulose membranes. The membranes were blocked with 5% non-fat dry milk in phosphate-buffered saline (PBS) with 0.1% Tween-20 (PBS-T) for 1 hour at room temperature. They were then incubated with primary antibodies against the nuclear components (nucleolin, histone H1, PABPN1, SFPQ, NF90, NF-κB, nucleophosmin, and SUMO proteins) overnight at 4°C. After washing, the membranes were incubated with horseradish peroxidase-conjugated secondary antibodies for 1 hour at room temperature. The protein bands were visualized using an enhanced chemiluminescence (ECL) detection system.

RNA Isolation and Quantification

To assess the role of nuclear interactions in viral RNA replication, total RNA was extracted from infected cells using TRIzol reagent according to the manufacturer's protocol. The RNA was reverse-transcribed to cDNA using random primers and reverse transcriptase. Quantitative PCR (qPCR) was conducted to measure DENV RNA levels, and the data were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an internal control.

RESULTS AND DISCUSSION

The results of this research revealed significant interactions between the Dengue virus (DENV) core protein and various nuclear components, each playing a critical role in virus replication and pathogenesis:

Nucleolin: The DENV core protein was found to interact with nucleolin, facilitating its transport to the nucleolus. This interaction enhanced viral RNA replication by optimizing the environment within the host cell. Additionally, nucleolin's alteration of host cell functions contributed to viral pathogenesis, leading to disruptions in cellular homeostasis.

Histone H1: The DENV core protein bound to histone H1, which promoted chromatin remodeling. This modification was necessary for efficient viral replication, as it created a more conducive environment for viral genome synthesis. The interaction also led to changes in host gene expression, affecting cell survival and immune responses, further exacerbating disease progression.

Poly(A)-binding protein nuclear 1 (PABPN1): The DENV core protein formed complexes with PABPN1, which stabilized viral RNA within the nucleus. This stabilization played a pivotal role in viral genome replication. Moreover, the disruption of normal RNA processing and transport by PABPN1 contributed to disease symptoms, including impaired cellular functions.

Splicing factor proline and glutamine-rich (SFPQ): The DENV core protein associated with SFPQ, modulating the alternative splicing of host pre-mRNAs. This alteration optimized the cellular environment for viral replication. Furthermore, SFPQ's interference with normal cellular functions led to apoptosis and inflammation, aggravating disease severity.

Nuclear factor 90 (NF90): The DENV core protein interacted with **NF90**, enhancing the stability and translation of viral RNA. This interaction contributed significantly to viral replication. Additionally, the manipulation of NF90 by the virus affected host antiviral responses, allowing the virus to evade immune detection.

Nuclear factor kappa light chain enhancer of activated B cells (NF-κB): The DENV core protein activated the NF-κB signaling pathways, promoting viral replication by upregulating genes involved in viral genome synthesis. This activation induced strong inflammatory responses, which contributed to severe manifestations of the disease, including increased immune-mediated damage.

Nucleoprotein (Nucleophosmin/B23): The DENV core protein co-localized with nucleophosmin, supporting the assembly of viral replication complexes. This co-localization caused a redistribution of nucleophosmin within the cell, disrupting normal cellular processes and contributing to viral pathogenesis.

Small ubiquitin-like modifier (SUMO) proteins: The DENV core protein was modified by SUMOylation, which influenced the localization and function of viral proteins, ultimately enhancing replication. The SUMOylation of viral proteins also altered host protein functions, contributing to immune modulation and the pathogenesis of the disease.

Overall, the research demonstrated how these interactions between the DENV core protein and nuclear components were integral to both virus replication and the development of severe disease symptoms.

Table 1. Representation of the characterization of the nuclear components that interact with the DENV core protein, focusing on their significance in virus replication and pathogenesis.

Nuclear Component	Interaction with DENV Core Protein	Significance in Virus Replication	Significance in Pathogenesis
Nucleolin	The DENV core protein interacted with nucleolin.	It facilitated the transport of the DENV core protein to the nucleolus, enhancing viral RNA replication.	It altered host cell functions, contributing to pathogenesis.
Histone H1	The DENV core protein bound to histone H1.	It promoted chromatin remodeling, which was necessary for efficient viral replication.	It led to changes in host gene expression, affecting cell survival and immune response.
Poly(A)-binding protein nuclear 1 (PABPN1)	The DENV core protein formed complexes with PABPN1.	It stabilized viral RNA within the nucleus, aiding in viral genome replication.	It disrupted normal RNA processing and transport, contributing to disease symptoms.
Splicing factor proline and glutamine-rich (SFPQ)	The DENV core protein associated with SFPQ.	It modulated the alternative splicing of host pre-mRNAs, optimizing the cellular	It interfered with host cellular functions, leading to apoptosis and inflammation.

		environment for viral replication.	
Nuclear factor 90 (NF90)	The DENV core protein interacted with NF90.	It enhanced the stability and translation of viral RNA.	It affected host antiviral responses and contributed to immune evasion.
The nuclear factor kappa light chain enhancer of activated B cells (NF-κB)	The DENV core protein activated NF-κB signaling pathways.	It promoted viral replication by upregulating genes involved in viral genome synthesis.	It induced inflammatory responses, contributing to severe disease manifestations.
Nucleoprotein (Nucleophosmin/B23)	The DENV core protein co-localized with nucleophosmin.	It supported the assembly of viral replication complexes.	It caused redistribution of nucleophosmin, disrupting normal cellular processes.
Small ubiquitin-like modifier (SUMO) proteins	The DENV core protein was modified by SUMOylation.	It influenced the localization and function of viral proteins, enhancing replication.	It altered host protein functions, contributing to immune modulation and pathogenesis.

In this research, the interaction between the Dengue virus (DENV) core protein and various nuclear components was critical for understanding its role in viral replication and pathogenesis. Several key interactions were identified, each contributing to different aspects of the viral life cycle and the onset of disease symptoms. The DENV core protein was found to interact with nucleolin, which facilitated its transport to the nucleolus. This interaction enhanced viral RNA replication by optimizing the localization of the DENV core protein within the cell. Studies by Kaneko et al. (2019) indicated that nucleolin plays a significant role in modulating the replication process of flaviviruses, including DENV, by altering the host cell's normal functions, thereby contributing to the virus-induced pathogenesis . The disruption of nucleolin functions likely affected ribosomal biogenesis and other nucleolar activities, intensifying disease progression. The DENV core protein bound to histone H1, a linker histone involved in chromatin structure regulation. This interaction promoted chromatin remodelling, a process necessary for efficient viral replication. Histone modifications, as demonstrated by Xu et al. (2020), have been linked to enhanced viral genome accessibility, enabling the DENV core protein to manipulate the host's transcriptional machinery. In doing so, the virus altered host gene expression, impacting both cell survival and immune responses, further contributing to disease manifestations. The interaction between the DENV core protein and PABPN1 was essential for stabilizing viral RNA within the nucleus. This stabilization directly supported the replication of the viral genome. According to research by Silva et al. (2018), the formation of complexes between viral proteins and PABPN1 disrupted normal RNA processing and transport, causing an accumulation of misprocessed RNAs, which contributed to the symptoms associated with severe dengue .

The DENV core protein associated with SFPQ, a splicing factor involved in the regulation of pre-mRNA splicing. This interaction was crucial for modulating alternative splicing events, which optimized the host cell environment for viral replication. Zhang et al. (2021) demonstrated that alternative splicing alterations, induced by the DENV core protein, led to aberrant expression of host genes involved in apoptosis and inflammation, exacerbating the disease condition. The DENV core protein interacted with NF90, enhancing the stability and translation of viral RNA. NF90 has been shown to act as a regulator of viral replication by binding to viral RNAs. Research by Li et al. (2020) indicated that NF90's interaction with DENV core protein contributed to the virus's ability to evade host antiviral defenses by modulating RNA stability, thus promoting persistent viral infection. The DENV core protein activated NF-κB signaling pathways, promoting viral replication by upregulating genes involved in viral genome synthesis. This activation also induced inflammatory responses, as reported by Muller et al. (2019), where NF-κB played a dual role in promoting replication while contributing to immune system dysregulation, often leading to severe manifestations like dengue hemorrhagic fever and dengue shock syndrome. The DENV core protein was co-localized with nucleophosmin (NPM1/B23), a nucleolar phosphoprotein involved in ribosome biogenesis. This co-localization supported the assembly of viral replication complexes. Wang et al. (2020) showed that the redistribution of nucleophosmin, induced by DENV core protein, disrupted normal cellular functions, further implicating the core protein in altering host cell homeostasis and contributing to viral pathogenesis. The DENV core protein underwent SUMOylation, a post-translational modification that influenced the localization and function of viral proteins. SUMOylation of the core protein enhanced its replication capacity by altering host protein interactions. Shen et al. (2021) reported

that SUMOylation also played a role in immune evasion by modulating host antiviral responses, thus contributing to viral persistence and pathogenesis.

CONCLUSION

In conclusion, these interactions between the DENV core protein and various nuclear components were essential for optimizing viral replication and facilitating immune evasion, which, in turn, contributed to the overall pathogenesis of dengue. Understanding these molecular interactions provided critical insights into potential therapeutic targets for disrupting viral replication and reducing disease severity.

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