In silico characterization of potentials *κB* binding sequences in miRNAs associated with severe dengue

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Abstract (300 word limit)

Statement of the Problem: Progression to severe dengue (SD) is associated with an exacerbated inflammatory response, in which nuclear factor-κB (NF-κB) plays a crucial role in regulating pyroptosis. This study aims to identify NF-κB molecular targets with potential prognostic value in DENV infection. Methodology & Theoretical Framework: An integrated bioinformatics pipeline was employed to map signaling pathways and systematically identify and characterize NF-κB binding sequences in target genes of interest (UCSC Genome Browser, FIMO, Clustal Omega, Alibaba 2.0, TargetScan, ShinyGO, and Cytoscape). Findings: We selected six miRNAs associated with SD (miR-148a-3p, miR-125a-5p, miR-1303, miR-155, miR-223-3p, and miR-21) and NF-κB-regulated genes. In both miRNA promotors and NF-κB-regulated gene promotors, a high density of κB sequences were found in the promoter region, particularly in TNFα, GSDMD, miR-148a-3p and miR-125a-5p. The κB sequences identified in both groups contain Sp1-binding motifs; this characteristic promotes exacerbated activation of the cytokine cascade. Therefore, the high density of Sp1 near the κB sequences may be key to these miRNAs' overexpression. The target genes of these miRNAs are associated with cell death and cytokine cascade activation, with miR-148a-3p and miR-125a-5p having more targets. Cell death and cytokine production in immune cells are crucial features of SD. Conclusion & Significance: NF-κB acts as a central hub in orchestrating pyroptosis and the expression of pyroptosis-related miRNAs. miR-148a-3p and miR-125a-5p represent candidate prognostic biomarkers for SD, warranting further clinical validation.

Image

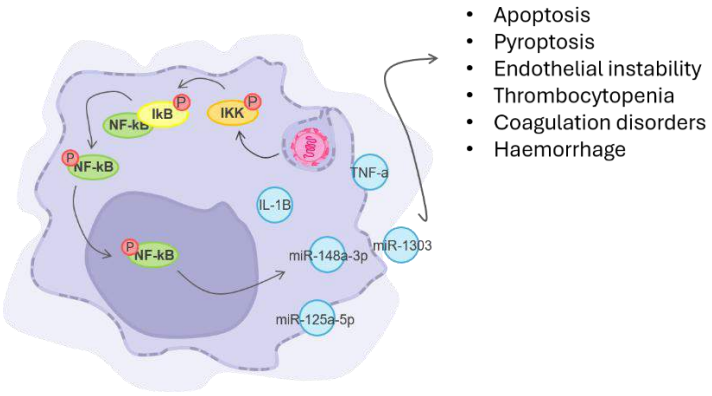


Figure 1. Signaling cascade leading to NF-κB activation by DENV. NF-κB activation promotes the expression of miRNAs and genes associated with cell death, leading to the characteristic signs and symptoms of SD.

Recent Publications (minimum 5)

1. Jing Q, Wang M. Dengue epidemiology. Glob Health J. 2019;3(2):37-45. doi: 10.1016/j.glohj.2019.06.002.
2. Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev. 2017;277(1):61-75. doi: 10.1111/imr.12534.
3. Pan P, Zhang Q, Liu W, Wang W, Yu Z, Lao Z, et al. Dengue Virus Infection Activates Interleukin-1β to Induce Tissue Injury and Vascular Leakage. Front Microbiol. 2019;10:2637. doi: 10.3389/fmicb.2019.02637.
4. Wu MF, Chen ST, Yang AH, Lin WW, Lin YL, Chen NJ, et al. CLEC5A is critical for dengue virus-induced inflammasome activation in human macrophages. Blood. 2013;121(1):95-106. doi: 10.1182/blood-2012-05-430090.
5. Nanda JD, Ho TS, Satria RD, Jhan MK, Wang YT, Lin CF. IL-18: The Forgotten Cytokine in Dengue Immunopathogenesis. J Immunol Res. 2021;2021:8214656. doi: 10.1155/2021/8214656.
6. Harun N, Leow CH, Kamarulzaman EE, Wahab HA, Vignesh R, Rasul A, et al. Assessing the potential of NS2B/NS3 protease inhibitors biomarker in curbing dengue virus infections: In silico vs. In vitro approach. Front Cell Infect Microbiol. 2023;13:1061937. doi: 10.3389/fcimb.2023.1061937.
7. Bannazadeh Baghi H, Bayat M, Mehrasa P, Alavi SMA, Lotfalizadeh

MH, Memar MY, et al. Regulatory role of microRNAs in virus-mediated inflammation. J Inflamm (Lond). 2024;21(1):43. doi: 10.1186/s12950-024-00417-7.

8. Markopoulos G, Roupakia E, Tokamani M, Alabasi G, Sandaltzopoulos R, Marcu K, et al. Roles of NF-κB Signaling in the Regulation of miRNAs Impacting on Inflammation in Cancer. Biomedicines. 2018;6(2):40. doi: 10.3390/biomedicines6020040.

9. Sheedy FJ. Turning 21: Induction of miR-21 as a Key Switch in the Inflammatory Response. Front Immunol. 2015;6:19. doi: 10.3389/fimmu.2015.00019.

Photograph

Biography (150 word limit)

Bt. Atenas Cortes Martell is a master's student with an academic interest in molecular biology and in understanding genetic and molecular mechanisms related to human health. She may participate in bioinformatics analyses and scientific communication activities within academic institutions. Her work is expected to incorporate systems biology and interactome-based approaches, using computational tools for target gene prediction and biological pathway analysis. This integrative perspective could contribute to a broader understanding of the molecular mechanisms involved in dengue pathophysiology and support the exploration of potential biomarkers or regulatory pathways of biomedical

Erick Obed Martinez Herrera, MSc, PhD, has been affiliated with the Instituto Politécnico Nacional since 2018. He maintains an active role in several postgraduate programmes, namely the Master's in Health Sciences (MACISA), the Specialisation in Medical-Surgical Emergencies (UMQ), and the Doctorate in Medical Research (DIM). Within MACISA, his contributions to curriculum development include designing a novel academic programme and comprehensively revising an existing syllabus. These academic responsibilities are undertaken at the Section of Postgraduate Studies and Research within the Higher School of Medicine, National Polytechnic Institute (IPN).

Fernando Guadalupe Bastida Gonzalez, MSc, PhD: Head of the State of Mexico Public Health Laboratory (LESP) and a Level 1 Member of the National System of Researchers (S.N.I.). His research investigates infectious agents and has resulted in five publications in JCR-indexed journals and three science communication articles. Through collaborations with prominent universities (UAEM, UAM, IPN), he actively contributes to capacity building, mentoring nine undergraduate and master's students, as well as two current PhD candidates. Dr Bastida Gonzalez completed a research fellowship at the US Centers for Disease Control and Prevention (CDC), focusing on ante-mortem rabies virus (RABV) detection. His research contributions were also recognised with international awards in 2012 and 2015. Holding extensive national and international certifications (CDC, PAHO) in pathogen handling and infectious disease management, he currently directs the LESP, overseeing an InDRE-certified facility for the molecular diagnosis of SARS-CoV-2 via real-time PCR.

Paola Zarate Segura MSc/PhD. has been affiliated with the Instituto Politécnico Nacional (IPN) since 2004, initially at the interdisciplinary Unit of Biotechnology and later at the Escuela Superior de Medicina. She is a Level I member of Mexico's National System of Researchers (SNII II) and currently serves as Full Professor (Titular C). She participates in the Master's Program in Health Sciences and the Doctoral Program in Medical Research (DIM), both recognized within the PNPC framework, and currently coordinates the DIM program. Her research focuses primarily on infectious diseases and molecular biology, with contributions to multidisciplinary biomedical projects. She has completed a research stay at the U.S. Centers for Disease Control and Prevention (CDC) and has received international recognition for work related to infectious diseases and synthetic biology.

Notes/Comments: