

Review

The Putative Roles and Functions of Indel, Repetition and Duplication Events in Alphavirus Non-Structural Protein 3 Hypervariable Domain (nsP3 HVD) in Evolution, Viability and Re-Emergence

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Citation: Abdullah, N.; Ahemad, N.; Aliazis, K.; Khairat, J.E.; Lee, T.C.; Abdul Ahmad, S.A.; Adnan, N.A.A.; Macha, N.O.; Hassan, S.S. The Putative Roles and Functions of Indel, Repetition and Duplication Events in Alphavirus Non-Structural Protein 3 Hypervariable Domain (nsP3 HVD) in Evolution, Viability and Re-Emergence. *Viruses* **2021**, *13*, 1021. <https://doi.org/10.3390/v13061021>

Academic Editor: Brian Geiss

Received: 31 January 2021

Accepted: 4 May 2021

Published: 28 May 2021

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Abstract: Alphavirus non-structural proteins 1–4 (nsP1, nsP2, nsP3, and nsP4) are known to be crucial for alphavirus RNA replication and translation. To date, nsP3 has been demonstrated to mediate many virus–host protein–protein interactions in several fundamental alphavirus mechanisms, particularly during the early stages of replication. However, the molecular pathways and proteins networks underlying these mechanisms remain poorly described. This is due to the low genetic sequence homology of the nsP3 protein among the alphavirus species, especially at its 3' C-terminal domain, the hypervariable domain (HVD). Moreover, the nsP3 HVD is almost or completely intrinsically disordered and has a poor ability to form secondary structures. Evolution in the nsP3 HVD region allows the alphavirus to adapt to vertebrate and insect hosts. This review focuses on the putative roles and functions of indel, repetition, and duplication events that have occurred in the alphavirus nsP3 HVD, including characterization of the differences and their implications for specificity in the context of virus–host interactions in fundamental alphavirus mechanisms, which have thus directly facilitated the evolution, adaptation, viability, and re-emergence of these viruses.

Keywords: alphavirus; nsP3; HVD; indel; repetition; duplication; mutation; evolution; phosphorylation; emergence

1. Introduction

The *Alphavirus* genus belongs to the *Togaviridae* family, together with *Rubivirus* and unclassified *Togaviridae* genera. To date, 32 different *Alphavirus* species have been identified [1], which are globally distributed across all continents except Antarctica. Besides being classified based on their antigenic characteristics, alphaviruses are also categorized as being either New World (NW) or Old World (OW) alphaviruses based on their E1 protein genetic diversity and the geographic locations where they were first isolated [2–6].