ORF3a mutations: an adaptive advantage for SARS-CoV-2 pathogenecity

Sougata Niyogi1*, Parinita Majumdar

1Dinabandhu Andrews Institute of Technology and Management, Kolkata

***Corresponding author: Sougata Niyogi**, Dinabandhu Andrews Institute of Technology and Management; E- Sougata.niyogi@daitm.org.in

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Abstract

The outbreak of severe acute respiratory syndrome in November 2019 resulted in a global public health emergency which warrants investigation of the virulence and pathogenecity of SARS-CoV-2. The reasonably higher mutation rate in SARS-CoV-2 led to the emergence of its numerous genetic variants which is likely to be responsible for COVID-19 associated morbidity and mortality. Mutations in ORF3a protein could modulate viral pathogenecity by interfering with host immune response and apoptotic pathways.

Commentary

With the emergence of youngest Coronaviridae family member at Wuhan province of Central China in November 2019, enormous number of SARS-CoV-2 genetic variants are reported world-wide [1-3]. Considerably huge RNA genome ~30kb, the largest among RNA viruses and poor fidelity of RNA dependant RNA polymerase (RdRp) might have accounted for the heightened mutation rate in SARS-CoV-2 [3]. In addition to the structural proteins, SARS-CoV-2 genome encodes eight accessory proteins of which 274 amino acid containing ORF3a protein is the largest one with predicted three transmembrane regions and six functional domains [1]. ORF3a encodes an ion channel protein and is implicated in host inflammatory responses through the activation of innate immune receptor NLRP3 (NOD, LRR and pyrin domain containing 3) inflammasome (Shah, 2020). NLRP3 mediated maturation of pro-inflammatory cytokines, interleukin- - IL-18 trigger secretion of downstream mediators of inflammation including IL6, tumor necrosis factor (TNF), prostaglandins and leukotrienes. This unrestrained release of pro-inflammatory cytokines hallmark of SARS-CoV-2 pathogenesis. Moreover, ORF3a induces apoptosis which is an important host antiviral strategy to regulate the viral infection [4]. Thus differential mutations in ORF3a protein are likely to determine the virulence of SARS-CoV-2 due to intervening apoptotic and inflammatory response pathways in varied viral isolates. Indeed, ORF3a mutation was correlated with higher mortality rate in infected individuals [2]. ORF3a protein is also predicted to be involved in host immune responses mediated by various signaling pathways including JAK-STAT, chemokine and cytokine related pathways [2]. A total of 51 non-synonymous amino acid substitutions were observed among 2782 genetic isolates and the domain III of ORF3a which is involved in ion channel formation harboured the maximum number of mutations [5]. Whether these mutations in domain III of ORF3a aggravate NLRP3 mediated inflammatory response need to be investigated. Thus it is possible that mutation in ORF3a protein could be an adaptive response