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Review

RNA enigma: “From origin of life to novel Coronavirus-COVID-19”

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ABSTRACT

Recent events of the viral catastrophe have shown the rapidity of spread of new disease through emergence of virulent strains. Proper control measures can be developed only through understanding the evolution of virulence in RNA viruses. To understand the evolution of this novel Coronavirus, COVID-19, it is imperative to delineate the evolution of RNA, its transformation into first life forms, the steady and continuous evolution and emergence through modification in their genome and nevertheless the natural selection. This review will throw light on these aspects to understand the possible origin of COVID-19 to control and eradicate this viral outbreak.

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1. Introduction

In any organism, the nucleic acids (DNA and RNA) and proteins play a vital role in reproduction and sustainability of life. In general, DNA stores the genetic information which is translated by RNA and the proteins serve as drivers of cellular processes. However, the thought of life started from RNA was valid to some extent since RNA could serve both as genetic coding material and cat-

alyzechemical reactions (Bernhardt, 2012; Gilbert, 1986) and is a crucial element in many of the deadly viruses dominating the eukaryotes with enormous diversity (Wolf et al., 2018). Scientists suggests life could have started around 4.1 billion years ago based on Zircon data (Bell et al., 2015). Mojzsis claims that after the impact of planetesimal form and a brief period of cooling, “at 4.4 billion years ago, there are settled niches for the propagation of life” (Mojzsis et al., 2001). These thoughts lead to a conclusion that simple organic molecule began to form and in presence of hydrogen, those molecules would have linked up to form RNA, the essential of emergence of life.

2. Evolution of RNA viruses

Viruses being the most abundant biological entities on earth which is distributed everywhere might have played important role

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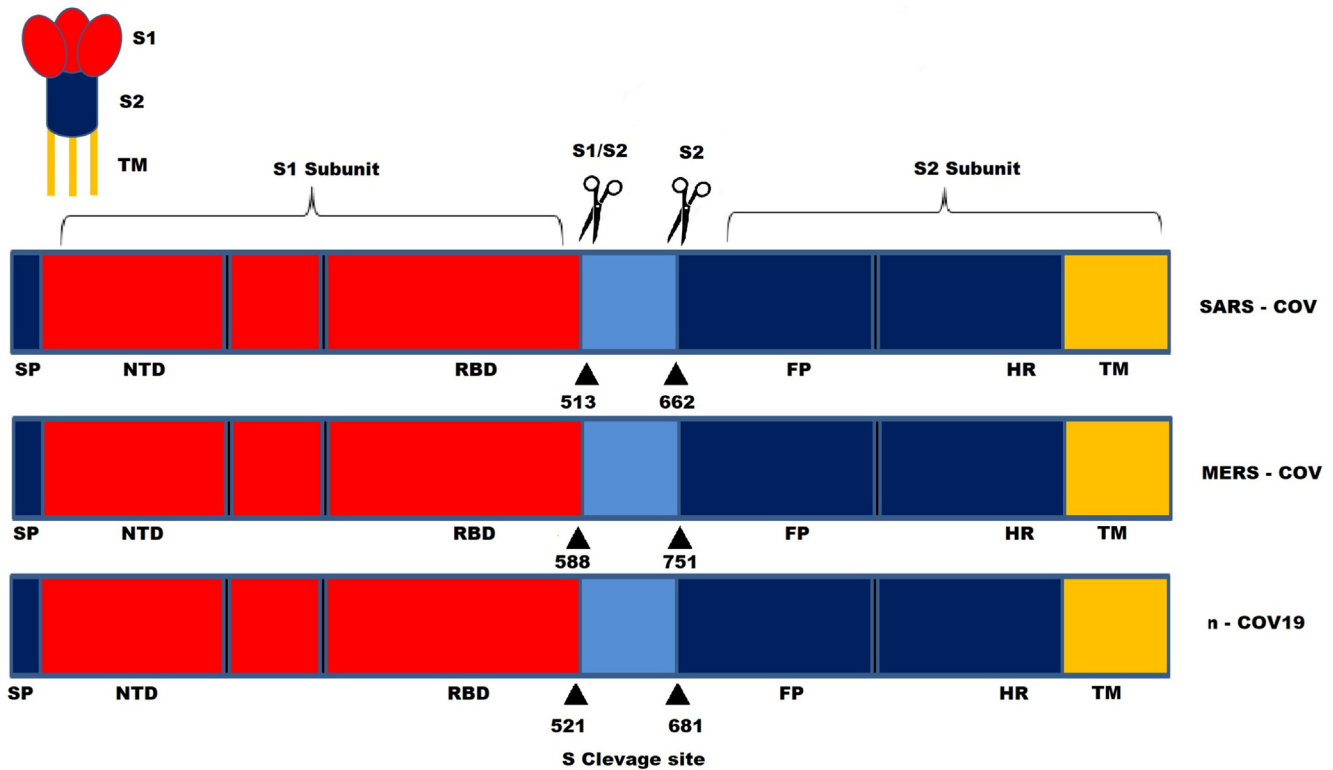


Fig 1. Divergence of Spike protein of Covid-19 to other related species (S1- Receptor binding Subunit, S2- Membrane fusion Subunit, TM- Transmembrane Anchor, NTD- N-Terminal Domain, RBD- Ribosomal Binding Domain, FP- Fusion Peptide, HR- Heptad Repeat region).

in origin of life during evolution. Viruses have been proven to be the actuators of evolution (Villarreal and Witzany, 2010). Mutations are building blocks of most of the evolution which causes variations that favours natural selection and emergence of novel traits (Baer, 2008). RNA viruses are the most fascinating microbe to study mutation rates as they encode their replication machinery and can optimize their mutation rates. The ability of RNA viruses to emerge in novel hosts and to exhibit resistance is due to their ability to rapidly change their genome (Vignuzzi et al., 2006; Lafforgue et al., 2011; Duffy, 2018). The analysis of metaviromics data resulted in identification of universal gene among RNA viruses as RNA dependent RNA polymerase (RdRp). The multipotent enzyme, RdRp hosted in Negative Strand RNA viruses responsible for grave viral diseases like Ebola, Lassa fever, Measles, Influenza and Rabies help in transcription and replication of viral genomes in the host. The research also revealed there is excessive gene exchange between diverse viruses and horizontal viral transfer between distantly related hosts (Wolf et al., 2018).

The positive strand RNA viruses use the simplest genomic strategy and represent the primary pool of RNA viruses. Genetic exchange and gene shuffling are the important factors in evolution of RNA viruses (Koonin et al., 1993) and structural and replication modules have been repeatedly shuffled during their evolution. Also horizontal spread of gene (Dolja and Koonin, 2018) had led to major change in viral lifestyle including adaptation of viruses to newer hosts. The results of wolf et al on evolutionary analysis revealed the conserved nature of RdRp and some other domains especially in picornavirus super group whose members can infect a wide variety of hosts viz., protists, fungi, plants, invertebrates and vertebrates. Evolutionary reconstruction studies suggest that the common ancestor of eukaryotic + RNA viruses were simple viruses that encodes only RdRp, the first enzyme (Farias et al., 2017) but later involved independent acquisition of distinct helicases to form complex + RNA genome. The evolution also favoured

gene module exchange among different viruses of distantly related hosts.

3. Possible origin of COVID-19

Coronaviruses are important pathogens of human and animals with extraordinary long RNA genome. They are positive sense single stranded RNA (+SS RNA) virus with 27 to 32 kb genome. The first human coronavirus was isolated and cultured in 1960s from nasal discharge from people with common cold. Although 4 major categories of coronavirus exists viz. alpha (α -corona), beta (β -corona), delta (δ -corona) and gamma (γ -corona), only α and β Coronaviruses infect humans. To date, 7 human Coronaviruses have been identified - HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, MERS-CoV and recently nCoV-19 or COVID-19. Coronaviruses are zoonotic and rarely animal coronavirus can evolve and infect human. Previously, SARS-CoV and MERS-CoV transmitted to human from animal sources and was a leading cause for death of many people which accounts to 10% and 30% of mortality respectively in infected people. The infectivity and spread of these viruses in faster rate have taught the lesson to take precautionary measures towards the recent COVID-19 outbreak. Human-human transmission has accelerated the spread of COVID-19 outbreak and its pandemic nature. The transmission of the virus, 2019-nCoV occurs primarily through the respiratory droplets produced during sneezing and coughing of infected person and further transmission occurs through close contact with infected individual (reviewed in Ullah et al., 2021). The transmission of these viruses from symptomatic and asymptomatic person is alike and it's alarming that the spread is enhanced through close contact with asymptomatic person while symptomatic persons could have been identified and isolated but not the case with the former. This created a panic situation and many countries called for curfew for the containment of viral spread.

Coronaviruses have an unusual replication involving two step processes: Initially the largest ORF called replicase is translated into series of enzymes and then sub genomic mRNAs are transcribed and subsequently used for translation of structural and accessory proteins from downstream ORFs that forms the new viral particles (Graham et al., 2008). COVID-19 or 2019-nCoV, a new human infecting β -coronavirus is identified as a divergent from SARS-CoV, whose close related virus available in Genbank was bat SL-CoVZC45 (Accession No.MG772933) and SARS-like β -coronavirus of bat origin (Accession No. MG772934) bat-SL-CoVZXC21 (Lu et al., 2020). It was also identified that most of the proteins encoded by 2019-nCoV exhibited high sequence similarity with bat - derived coronavirus with notable exception in spike protein and protein 13 with 80% and 73.2% sequence identify. It is also noted that 2019-nCoV were less genetically similar to SARS-CoV (79%) and MERS-CoV (50%). Another important distinctness which indicates the novelty of this virus is in its RdRp. Besides conserved architecture of core polymerases nsp12 (RdRp of nCov) posses β hairpin domain at the N terminus (Gao et al., 2020). Although concrete evidence available for bat as reservoir of coronaviruses in general and COVID-19 in particular, involvement of an intermediate host between human and bats are suspected. The spike phylogeny of COVID-19 shares homology with bat SARS-like coronaviruses and uses similar receptor (ACE2 receptor) to infect lung cells (Ge et al., 2013; Wan et al., 2020; Cao et al., 2020). COVID-19 might use receptor binding domain (RBD) fragment of S protein to bind to the ACE2 receptor was delineated by characterization of RBD of nCoV-19 and subsequent experiment demonstrated to show the binding ability to ACE2 receptor (Tai et al., 2020). Mutation of spike protein and nucleocapsid protein could be correlated to the higher infectivity and enhanced pathogenicity of nCoV-19 (Benvenuto et al., 2020). The divergence of Spike protein of Covid-19 to other related species is shown in Fig. 1 which shows the variability in cleavage sites among the human coronaviruses. Recombination is a frequent event seen in coronaviruses (Su et al., 2016) but phylogenetic analysis revealed the occurrence of recombinations only in the bat coronaviruses and recombination is not the probable reason for emergence of this virus COVID-19.

Based on the genomic data, two possible scenarios were proposed for origin of COVID-19 (Andersen et al., 2020). In one, the virus would have evolved to the pathogenic form through natural selection in a non-human host and jumped to human. Since the reservoir of the virus was traced back to bat but no concrete evidence for direct transmission from bat to human. In this case, the distinctive feature of spike protein RBD would have evolved to become pathogenic. Evidence also suggests that mutations in spike gene could have occurred in late November 2019 triggering the jump to human (Angeletti et al., 2020; Cascella et al., 2020). In another, the non - pathogenic form of the virus would have jumped to human from some animal host (yet to be found out) and evolved to the current pathogenic form within human host. The possibility of evolution of a virulent cleavage site in nCoV-19 within human host before epidemic was also possible but chances of this type of non-pathogenic transmission to human and evolving properties of infection is lower compared to the previous scenario. But at the same time, the transmission of pathogenic form from animal source to human is to be considered seriously, as the unknown intermediate can serve as a reservoir of this pathogenic virus raising the possibility of future outbreaks.

4. Conclusion

With sequences from various geographical regions are submitted every day, the complete perspective of evolution and emergence of this virus could be illustrated and achieved sooner.

However this will give a comprehensive review of the role of RNA in origin and evolution. Genome mining will provide us with a better insight to contain and eradicate this viral catastrophe.

Author Contributions

Both the authors contributed equally in construction, revision and approval of this manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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