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Review Article

Accumulation of Mutations with Time Reduces the Infectivity and Virulence of RNA Viruses: a Discussion on SARS-CoV-2

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Abstract

Higher the mutation rate higher is the possibility to evolve" and "higher the possibility to evolve higher is the possibility of extinction". I hypothesize that pharmacological acceleration of the rate of mutations in the viral progeny genomes would help to destroy the virus infectivity and/or virulence. It is clear from the history of viral diseases - with course of time virus progeny gain low to medium mutation that enhance virulence, and further accumulation of mutation in the subsequent progenies cause reduction of infectivity and/or loss of replicative potential. We know the nature of mutation is random though, statistically it happens. Since +ssRNA virus replication is catalyse by their own polymerase lacking proofreading activity, they have high mutation rate. The mutation data in current SARS-CoV-2 support its high mutation rate in the world implicating that its additional proof reading ability is not much effective. Enhancement of mutation in SARS-CoV-2 genome could be achieved by using nucleotide analogues with Pharma products (medicine) would be helpful to fight pandemic COVID-19.

Keywords: Infectivity; Virulence; COVID-19; SARS-CoV-2; Single-stranded positive-sense RNA (+ssRNA); RDRP; Remdesivir; Mutation

Introduction

Our knowledge from the textbook and current research says that RNA viruses have higher mutation rates (Figure 1A) [1,2]. Figure 1B depicts the rate of mutation versus genome size among the two close biological entities, the virus and bacteria [1]. It is our observation from the history of Spanish flue, SARS, MARS, etc. outbreaks; the infectivity (capability of entering into the host) and virulence (capability of production of new virion) of those viruses increase rapidly to a peak and then gradually fall down (Figure 1B). I discuss this phenomenon in terms of accumulation of defective mutation from the perspective of the respective virus. I am keeping away the host side from my discussion, the theory of heard immunity, particularly for these as vaccine is not available as of yet. Severe acute respiratory syndrome Coronavirus clade-2 (SARS-CoV-2) is a single-stranded positive-sense RNA, ss (+) RNA, virus, which upon infection cause Coronavirus Disease 2019 (COVID-19) public-health emergency [3]. SARS-CoV-2 belongs to the subgenus Sarbecovirus of the genus Betacoronavirus; nonetheless, genetically distinct from SARS-CoV with similar receptor-binding domain structure with key amino acid variation of several residues. Corona virus genome is composed of ~30 kb in length with 5'-cap structure and 3'-poly-A tail [4]. As stated elsewhere in numbers of reports about hospitalized adult patients with severe COVID-19, use of remdesivir (pro-analogue of adenosine triphosphate) appeared to have a favourable effect [5]. However, use of combined antiviral medicines also exerts curative measures, albeit severe toxic effects [6].

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Replication of RNA virus is mutation prone

Typical pattern of replication of ss (+) RNA viruses is that, after infection a major portion of its RNA is translated first by host ribosomal machinery to produce polyproteins, which are processed further to produce several non-structural proteins (nsps) of distinct function, including double membrane sphere formation, replication of the genome, production of structural proteins and packaging to individual virion. The replication process of RNA viruses is error prone due to lack of proof reading activity of their own replication machinery, the RDRP (RNA dependent RNA polymerase), and thus their mutation rates are high. RNA viruses yield offspring that differ by 1-2 mutations each from their parent and enhancement of this rate would cause for their extinction [7]. Inability to maintain their original genome facilitates them to grow in novel hosts escaping immune attack up to certain level. In polio- and influenza-virus higher mutation rate causes lethal mutagenesis. The exogenous mutagens may cause enough additional mutations, which are often deleterious, so that the progeny RNA viruses achieve lower fitness and eventually extinct from the environment. Earlier analyses on RNA virus mutation rates suggested that host cell metabolic environment normal to the virus put it just under the threshold for lethal mutagenesis; nonetheless, the selection for genetic diversity and other consequences of a high mutation rate push RNA viruses to near their catastrophic limits.

Mutation analyses of SARS-CoV-2 mutation

SARS-CoV-2 mutation analyses implicates high mutation rate despite additional proofreading factors. Nidovirales family members including toroviruses and roniviruses are notable exceptions as they have an RDRP-independent proofreading activity. This proofreading is thought to be a key factor in explaining how these viruses have lower mutation rate and bigger genomes (>26 kb) compared to other RNA

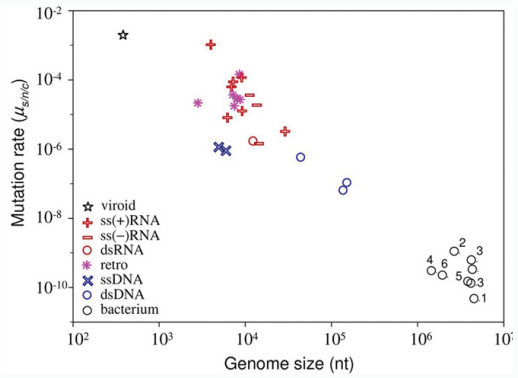

Figure 1A: Mutation rate of viruses: Sanjuán et al. [1] predicted the mutation rate of major virus groups as indicated in the plot. Mutation rate varies inversely with genome size and for ss (+) RNA viruses the rate is very high. In the plot there are values for two adjacent levels of biological entities, viroids and bacteria. The mutation rate is expressed as the number of substitutions per nucleotide per generation, defined as a cell infection in viruses (μs/n/c). [Adapted with permission from Sanjuán et al. [1], see also [2].

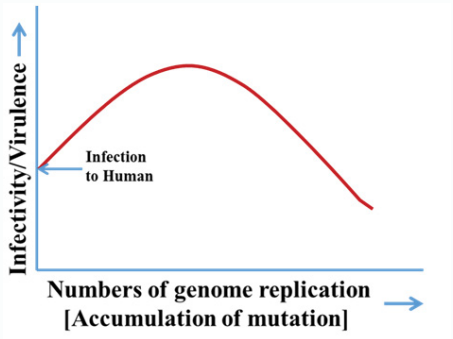

Figure 1B: viruses multiply 10^4 to 10^5 times in a healthy host cell till the nutrient supply exhausted. Number of virion produce in a human is very high. Accordingly, accumulation of mutation per transmission is naturally very high; considering the randomness of mutation one cannot predict which transmission dreadful. However, general trend of pandemics suggest that during the first phase the mutations enhance the infectivity and/or virulence and further mutations is detrimental to the virus itself to cope up with the host.

viruses. A project analysed 220 genomic sequences from the GISAID database derived from patients infected by SARS-CoV-2 worldwide from December 2019 to mid-March 2020; keeping SARS-CoV-2 genome from the Gen Bank database as reference [8]. They executed Genomes alignment exploiting Clustal Omega and verified statistical significance using Mann-Whitney and Fisher-Exact tests. The project successfully characterized eight novel repetitive mutations of SARS-CoV-2 genome at positions 1397, 2891, 14408, 17746, 17857, 18060, 23403 and 28881. Mutations in 2891, 3036, 14408, 23403 and 28881 positions are predominantly observed in Europe, whereas those located at positions 17746, 17857 and 18060 are exclusively present in North America. They detected a silent mutation in RDRP gene in England on February 9th, 2020, and an effective mutation in RDRP differing in amino acid composition emerged on February 20th, 2020 in Lombardy, Italy [8]. Viruses with RDRP mutation have a median of 3 point mutations [range: 2 to 5], otherwise they have a median of 1 mutation [range: 0 to 3] (p value <0.001).

Among the mutations in Coronavirus genome, D614G is notable. Very high mutations are categorized into 11 types/clades defining the first one from Wuhan as the ancestral (O type). Forster et al. [3] detected C28144T (ORF8: L>S), T8782C, T29095C, G26144T (ORF3a:G251>V). The A2a type of SARS-CoV-2 bears D614G non-synonymous mutation positioned in the S1-S2 joint, site specific for furin recognition, R667 [9]. Furin cleaves S protein essential for the entry of the virion into the host cell; experimental validation is essential if there is any role for this mutation. Maitra et al. [10] detected mutations in SARS-CoV-2 genome from COVID-19 patients of Eastern India. P323L mutation in RDRP, D614G in the Spike glycoprotein (S), nonsynonymous mutations G1124V in Spike (S), R203K, and G204R in the Nucleocapsid (N) protein was detected. G204R lies in the SR-rich region responsible for viral capsid formation. G1124V mutation is in the S2 domain responsible for viral fusion with the host cell membrane ACE2. They found intriguing correlation in between of COVID-9 patients' travel or contact history and these mutations. Mutations D614G (in SD domain) and G1124V (in S2 subunit) may have implications on structural stability of S protein. Two-amino acid substitutions (N479K/T487S) in the RBD of SARS-CoV-2 were also traced from Indian patients [10]. Shang et al. [11] described the SARS-CoV-2 spike protein's Receptor-Binding Domain (RBD)-ACE2 complexes. This work and others have resolved that, in general ACE2-binding pattern of the SARS-CoV-2 RBD is identical to that of the SARS-CoV RBD. Shang et al. [11] identified ACE2-binding ridge in SARS-CoV-2 RBD has a more compact conformation. Changes of several residues in the SARS-CoV-2 RBD stabilize two virus-binding hotspots at the RBD-ACE2 interface. These structural features of SARS-CoV-2 RBD increase its ACE2-binding affinity. They further demonstrated that, bat Coronavirus RaTG13, closely related to SARS-CoV-2, also makes complex with human ACE2. Other groups identified amino acid residues in the SARS-CoV-2 RBD that are essential for ACE2 binding [12,13]. Most of those are highly conserved or have similar side chain properties with those in the SARS-CoV RBD. This similarity in structure and sequence highly support convergent evolution between the SARS-CoV and SARS-CoV-2 RBDs for improved binding to ACE2 [11-13]. The data analysed by the crystallographers comparing SARS-CoV and SARS-CoV-2 structures of spike protein are from early infection [1]; recent data analysis [9,10] from the GISAID and other Gene Bank explores accumulation of more mutation implicating defective functions of spike protein, main protease (nsp5) and RDRP (nsp12). The most of the SARS-CoV-2 accessions from various countries are close cousins from China or USA. The samples studied up to mid April 2020 were collected at the early stage of the pandemic till end March 2020, which depicted aggressive mutations and these data has less noise compared to recent published genomes of complex spread background to India, Australia, Brazil, South Korea, Japan and Sweden. Jia et al. [14] analysed that RBD mutants with lower affinity already emerged.

Discussion and Conclusion

These findings suggest that the virus is accumulating mutation and may be SARS-CoV-2 evolving and in this context the contribution of the mutated RDRP could be exploited against COVID-19. To date, several drugs, including remdesivir targeted against RDRP and lopinavir-ritonavir targeted the main protease enzyme [5,6] are being employed for SARS-CoV-2 treatment. Some of the drugs have a predicted binding moiety in a SARS-CoV-2 RDRP hydrophobic cleft [15], which is adjacent to the 14408 mutation identified [9]. It is very important to characterize SARS-CoV-2 RDRP functional mutation in order to understand possible drug-resistance strains also [16].

In view of this and the concept, "higher the mutation rate higher is the possibility to evolve" and "higher the possibility to evolve higher

is the possibility of extinction" from the science of evolution [14], and lack of vaccine production in this scenario and the precise role that nucleotide analogues may play to induce higher and higher mutation, may be exploited to combat the disease COVID-19. The nucleotide/nucleoside analogues, including azacitidine may be very useful along with remdesivir [13,15].

Low to medium quantity of mutations is harmful [1,11-13] because those wouldn't cause sufficient damage to the main machineries, including main protease, the RDRP or structural proteins including spike RBD; however, accelerating the mutation rate can make the virus extinguish sooner. We cannot fix mutation in the desired location/points [1,7] for such dreadful pathogen; however, can enhance the possibility by enhancing the mutation rate [16-18]. It can be argued that virulence prone mutations would be enhanced by anti virals and would make the vaccine useless sooner as well, if it is available for protection in the near future. Hence, it is very promising to combat the SARS-CoV-2 by accelerating the mutation rates using nucleotide/nucleoside analogues as demonstrated for other RNA viruses [19]. Moreover, it is promising that enhanced mutation rate of SARS-CoV-2 is possible, because its proofreading accessory is not efficient and high rate of copy numbers similar to other RNA viruses [20]. This contribution presented the view of combined antiviral therapy including nucleotide/nucleoside analogues for COVID-19. After extinction of SARS-CoV, SARS-CoV-2 emerged; that another form may outbreak was predicted in the recent past by Carrasco-Hernandez et al. [21].

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