Mildness of Host-Induced Mutations in SARS-COV-2

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Abstract

Most mutations in SARS-COV-2 are not random but caused by the host intracellular antiviral mechanisms ("host editing"). Because of the host editing, almost half of the nucleotide mutations are C > U transitions.

This study observes that **none** of the 12 most dangerous mutations in the SARS-COV-2 spike of the major pre-Omicron variants included a C > U transition.

This observation and the existing body of knowledge support the proposition: **coronavirus RNA mutations, caused by the host editing, tend to be less dangerous than mutations from other causes**.

The main practical conclusion is that mutations introduced externally (such as by Molnupiravir) are more likely to cause dangerous variants. When evaluating mutagen's potential co create dangerous variants of coronavirus, the frequency of mutations caused by it should be compared to frequency of mutations NOT caused by host-editing.

Fig. 1. The most dangerous mutations in spike, RBD. T19R is not shown.

Spike RBD	Alpha	Beta	Gamma	Delta	Lambda	Mu	Spike RBD	Alpha	Beta	Gamma	Delta	Lambda	Mu	
K417T	0%	0%	96%	0%	0%	0%	A22812C	0%	0%	96%	0%	0%	0%	A>C
K417N	0%	92%	0%	0%	0%	8%	G22813U	0%	92%	0%	0%	0%	8%	G>U
L452R	0%	0%	0%	99%	0%	0%	U22917G	0%	0%	0%	99%	0%	0%	U>G
L452Q	0%	0%	0%	0%	99%	0%	U22917A	0%	0%	0%	0%	99%	0%	U>A
T478K	0%	0%	0%	99%	0%	0%	C22995A	0%	0%	0%	99%	0%	0%	C>A
E484K	0%	90%	97%	0%	0%	98%	G23012A	0%	90%	97%	0%	0%	98%	G>A
F490S	0%	0%	0%	0%	98%	0%	U23031C	0%	0%	0%	0%	98%	0%	U>C
N501Y	99%	90%	97%	0%	0%	98%	A23063U	99%	90%	97%	0%	0%	98%	A>U
D614G	100%	100%	100%	100%	100%	100%	A23403G	100%	100%	100%	100%	100%	100%	A>G
P681H	100%	0%	0%	0%	0%	100%	C23604A	100%	0%	0%	0%	0%	100%	C>A
P681R	0%	0%	0%	100%	0%	0%	C23604G	0%	0%	0%	100%	0%	0%	C>G

Introduction

APOBEC (a family of cytidine deaminases), AID (activation-induced deaminase), and ADAR (adenosine deaminases that act on RNA) are involved in innate and adaptive immunity [1].They are activated by interferon signaling[2] [3] [4] on invasion of pathogens, and they activate adaptive immunity. These deaminases inhibit the virus by multiple mechanisms, mostly not involving RNA editing [2]. This host editing is responsible for the excess of C > U[ii] transitions [2] [3] in coronavirus mutations. It is also responsible for the excess A > G transitions, but it is irrelevant. These host editing enzymes act as an

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[ii] **U** is equivalent of **T**. This paper is intended for various audiences.

additional source of mutations and might contribute to immune escape [5]. APOBEC is also involved in eliminating autoimmune antibodies [6]. See this review [4] for more information.

APOBEC is result of relatively recent evolution. There is only one APOBEC3 gene in mice and rats, usual subjects of lab experiments, six APOBEC3 genes in horses, and seven in humans [7]. Most mutations in SARS-COV-2 RNA are caused by the host editing. Without host editing (APOBEC), SARS-COV-2 mutation rates would be less than 0.05 per genome per cycle [6].

APOBEC & ROS host editing are responsible for the abundance of C > U mutations [6]. C > U constitute almost 50% of all nucleotide mutations (ref. [8] "*Rampant C→U Hypermutation in the Genomes of SARS-CoV-2 and Other Coronaviruses*").

Main Part

Hypothesis

Host editing mechanisms are usually triggered by interferon signaling about a viral infection. Thus, a higher rate of host editing mutations should be associated with a rapid and effective immune response. In addition, some or most host editing mutations are just side effects of the intracellular antiviral mechanisms, preventing viral RNA replication. A higher rate of such "side effect" host mutations is additionally associated with effective immune response. An effective immune response limits the viral load in a host and decreases the chances of the mutated virus propagating.

Thus, virus RNA mutations caused by host editing have much lower chances of transmission to other individuals and fixating. This conclusion is also supported by the logic of the evolutionary theory. Intracell anti-viral immunity evolved in vertebrates, and favors them, rather than species-jumping viruses.

Observational Confirmation

In agreement with other sources, (the *Annex, S. C-to-U Merck Trials*, calculated from refs. [9] [10]), Merck reported that 49.4% of all nucleotide mutations (including transitions, transversions, deletions, and insertions) in patients receiving placebo were C > U. The number is rounded to 50% for p-value calculations below.

Here, we consider only the most dangerous (or "major") variants before Omicron: VOCs Alpha, Beta, Gamma, Delta, and VOIs Lambda and Mu.

None of the problematic amino acid mutations in the S-protein gene are caused by C > U transition! See the *Annex, S. C-to-U variants*. External mutation causes must be examined.

If we consider the S-protein mutations by their impact and frequency, there will be:

MOC: E484K

MOI: K417T, K417N, L452R, N501Y, D614G, P681H, P681R

Other: T19R, L452Q, T478K, F490S

None of these 12 top spike mutations are caused by C > U transition (p-value = 0.0025).

Calculating according to W.H.O classification yields a similar, but less clear picture: 8 amino acid mutations in the S protein are declared mutations of interest (MOI) or and one (E484K) is declared a mutation of concern by W.H.O. Only one of them (obscure L18F) is caused by nucleotide transition C > U (p-value = 0.02)

In addition, among mutations associated with the major variants, only 20% (rather than expected 45-50%) of the nucleotide mutations in the S-protein of the major variants are C > U.

Discussion

This study observes that none of the dangerous mutations in the spike protein of the major pre-Omicron variants contain C > U mutation (p-value = 0.0025). This observation is in line with the fact that viral RNA mutations caused by host editing are less dangerous and less likely to propagate than mutations introduced by external sources.

The main practical conclusion is that excess mutations introduced externally (such as mutagen Molnupiravir) are more likely to cause dangerous variants. In other words, when evaluating potential ability of a mutagen to lead to the creation of dangerous variants, the number of mutations caused by it should be compared to number of mutations NOT caused by host-editing, which is at least 5 times lower.

Conclusion

Thus, not all mutation causes are equal. Mutations caused by host editing are less dangerous and less likely to propagate and cause major variants. Mutations caused by external sources are much more likely to lead to the creation of dangerous variants. Molnupiravir increases the number of coronavirus mutations 3 times per cycle, but the number of dangerous mutations will increase by 30 times per cycle. This is highly concerning and must be stopped before it is too late.

No Competing Interests

The author declares no competing interest. No funding was provided for this work.

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