Why Omicron Variant of SARS-CoV-2 is Less Fatal?

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The article published by Nie et al. addressed one of the two key questions regarding the Omicron variant of SARS-CoV-2, while the underpinning for the less deadly nature of the variant remains unexplained. The proteins of the Omicron variant have numerous mutations, notably several substitutions of other amino acids by lysine residues. Glycine and valine attract calcium and enhance the formation of stressful, insoluble, and stiff calcium oxalate. Lysine residues in proteins build up chloride via ionic bonds which solubilizes insoluble and rigid divalent salts. The aforementioned mutations have weakened the lethalness of the Omicron variant perhaps via a biochemical mechanism. Despite net gain in favorable mutations versus deleterious mutations, the overall valine plus glycine content is still high in the proteins of Omicron variant of SARS-CoV-2, which remains a public health concern.

The article written by Nie et al. pointed out that the higher infection potential of the Omicron variant of SARS-CoV-2 can be attributed to multivalent charge-charge interactions with anionic receptors.[1] This view has furthered our understanding on the etiology of COVID-19. However, their article has not delineated another important issue regarding this variant: why it is much less deadly than many other variants?[2]

The proteins of SARS-CoV-2 and SARS are generally over-represented in valine plus glycine.[3] The spike protein of the Omicron variant harbors several amino acid substitutions by lysine.[1] These features are biochemically intriguing due to the chemical attributes of amino acids which render this variant less lethal. Glycine and valine possess long carbonyl bond lengths and weakened carbonyl bonds that prompt carbonyl oxygen atoms to bind divalent cations such as calcium.[4] The generation of insoluble and stiff calcium salts such as calcium oxalate or/and calcium phosphate is very stressful and can trigger cell senescence as demonstrated in the studies of renal stones.[4] Oxalic acid was indeed enriched in the serum of SARS-CoV-2 patients.[5] The positively charged lysine residues attract anions such as Cl^- via ionic bonds which can solubilize insoluble and stiff salts.[4] The antagonism between insoluble salts and acids or strong anions is widespread in cells (Figure 1).[4,6] The basic amino acid arginine can bind calcium[7] enhancing the formation of stressful calcium oxalate, which explains the lethality

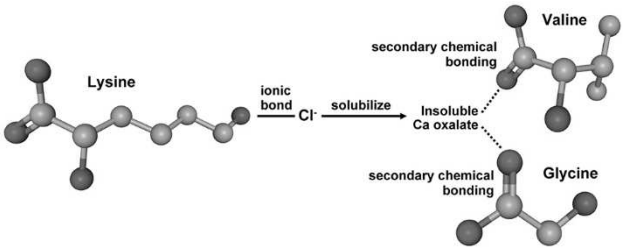

Figure 1. Biochemical antagonism between lysine and valine plus glycine.

associated with several arginine replacements in Delta variant of SARS-CoV-2.[1,2] There are a few scenarios on the origin of the Omicron variant including a potential zoonotic origin. One likely cause is that in the AIDS-prevalent South Africa, the mutation-prone HIV1 in a patient trigged the accelerated evolution of the SARS-CoV-2, by the hydrogen bonding-rampant HIV1 proteins as well as the hydroxyl oxygen atoms of ribose in RNA capable of hydrogen bonding, augmenting the formation of mutagenic strong acids such as HCl.[6,8]

Glycine toxicity has been extensively examined previously. Mortality rates were 71% after 1.5% glycine, 33% after normal saline and 0% in controls.[9] The amino-terminal domain harboring repeats of PHGGGWGQ in PrP^C protein displayed several sites which built up Cu^{2+} via glycine chelating.[10] Ca^{2+} ions were reported to help trap RGD tripeptide (arginine-glycine-aspartate) on both hydroxylated and nonhydroxylated rutile.[11] Calcium and zinc can be found in complexes with valinate and isovalinate.[10] Positive associations of hypocalcemia with mortality have been documented amidst COVID-19 pandemic.[12] An investigation revealed that a nine-residue peptide, VGGAVVTGV, is indispensable for the fibrillization and cytotoxicity of human alpha-synuclein.[10] SARS-CoV-2 N-protein interacts with α-Synuclein augmenting amyloid accumulation.[13] Lysine supplement has been demonstrated to be beneficial to heart disease sufferers, and high glycine plus valine is a hallmark of the causative factors of heart disease.[4] It is noteworthy that about 20–30% glycine plus valine was found in the toxic Aβ40 and Aβ42 peptides detected in the brains of

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Alzheimer's disease sufferers, and in some causative factors of amyotrophic lateral sclerosis, prion diseases and Limbic-predominant age-related TDP-43 encephalopathy.[4,10,14] Thus, high glycine plus valine content is a hallmark of numerous disorders and merits further investigations. Interestingly, glycine supplement displayed anticancer effects[15] which can be credited to its calcium binding property allowing the neutralization of mutagenic strong acids such as HCl, as single stranded DNA can draw protons via hydrogen bonding for the formation of acids.[4] Non-polar amino acid mutations in the proteins of a viral variant can be detrimental as they increase the insolubility of aggregates formed among glycine and valine residues in proteins and calcium oxalate.[10]

In a study on 5 year-olds and under which excludes the compounding of vaccination and past infections, the symptoms of Omicron infected patients were substantially less severe than those infected with the Delta variant.[16] Some vaccines have shown lower efficacy against the delta variant (B.1.617.2) and the omicron variant (B.1.1.529).[17] Booster shots with mRNA vaccines restored protection against the omicron variant (B.1.1.529).[17]

In summary, the biochemical attributes of specific amino acids have contributed to the lethality of SARS-CoV-2 proteins, and Omicron variant reduces the deadliness via net gain in favorable mutations.

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Conflict of Interest

The authors declare no conflict of interest.

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