EDITORIAL

MALARIA ENDEMICITY EFFECT ON COVID-19 PATHOPHYSIOLOGY: AN IN-SILICO PROTEIN-PROTEIN INTERACTION ANALYSIS

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The lower spread of COVID-19 in malaria endemic regions of world has been concluded in recent global COVID-19 data analysis. Scientists have compiled hypotheses about the relationships of these two infectious diseases; while some of those seem that have fully failed as malaria medications like Hydroxychloroquine were not effective in COVID-19 prevention. Our analysis of competition between ACE2 binding proteins as well as neutulizing SARS-Cov-2 antibodies revealed a similar structure to SARS-CoV-2 spike S1 protein in Plasmodium falciparum. Surprisingly, in an In-silico protein-protein interaction analysis, 20S proteasome alpha-4 subunit of Plasmodium falciparum had a better or equal binding affinity to ACE2 protein than SARS-CoV-2, based on a computational docking and MM/GBSA analysis. We hypothesized that prior encounter with Plasmodium falciparum in malaria endemic areas and the presence of asymptomatic variants of malaria in the body may render the human body to a competitive environment for SARS-CoV-2, as both infectious agents of malaria and SARS-Cov-2 may have a strong binding affinity to ACE2 protein.

Keywords: Malaria; COVID-19; Protein-Protein Interaction; Vaccination

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To Editor,

Plasmodium falciparum, as a malaria infection agent, is an evolutionary driving force that plays a critical role in shaping the human genome.[1] Previous studies have suggested plasmodium parasitemia with better prognosis of disease in other viral infections like in Ebola patients.[2] Some researchers have stated lower incidence of COVID-19 in malaria affected countries.[3,4] Malaria-endemic areas in Africa had fewer cases of COVID-19 in first months of the disease spread.[5–7] It has been shown that SARS-CoV-2 uses the same cell entry receptor as SARS-CoV, the Angiotensin-converting enzyme 2 (ACE2)[8] that may be also effective in malaria pathophysiology[9].

We were conducting a Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) analysis to predict binding free energies of possible proteins binding to Native Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2) [PDB ID: 1R42], in HawkDock database.[10] PDB ids containing structures of proteins as well as Structure of the SARS-CoV-2 spike S1 protein in complex with CR3022 Fab [PB ID: 6YOR], 2019-nCoV spike glycoprotein with a single receptor-binding domain up [PDB ID: 6VSB], Crystal structure of human angiotensinogen [PDB ID: 2WXW] were evaluated for free binding energy in association of ACE2. The best binding affinity was seen in 6YOR: A PDB ID, with the lowest free binding energy (Figure-1). A structural search through the PDB database with following query "*Structure Similarity WHERE (PDB ID = "6YOR" AND Chain ID = "A" AND Shape Match = "Strict")*", revealed 1 similar structure in Plasmodium falciparum species, which was the 6MUV PDB ID, the structure of the Plasmodium falciparum 20S proteasome in complex with two PA28 activators. Surprisingly, the 20S proteasome alpha-4 subunit of Plasmodium falciparum had a better or equal binding affinity to ACE2 protein than SARS-Cov-2 proteins (Figure-1) based on ANOVA analysis in SPSS software. Also, the 20S proteasome alpha-4 subunit of Plasmodium

falciparum had very higher binding affinity to ACE2 than Crystal structure of human angiotensinogen, a functional protein, closely related to ACE2's main function in the body.

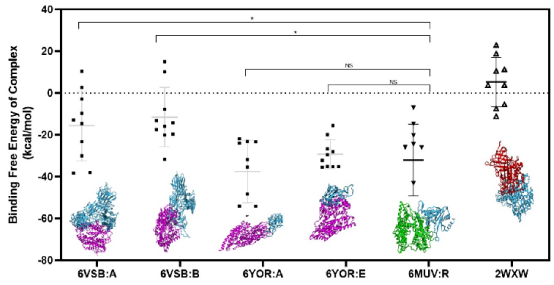

Figure-1: Binding free energy of evaluated PDB IDs

More negative binding energy stands for more affinity of complex drawn below the figure. Blue chains are ACE2 structure. Purples are SARS-Cov-2 related structures and Red one is the Angiotensin. *: significant difference in ANOVA analysis. NS: not significant difference. Graph is visualized by Graphpad prism software v.8. Protein interactions are visualized by HawkDock using PDB database.

These evidences show the possible hidden relationship between malaria endemic areas and their low COVID-19 prevalence. Plasmodium falciparum components may bind to ACE2 receptors, as previously shown in literature[9] and inhibit the SARS-COV-2. So, we hypothesed that previous confrontation of the Plasmodium falciparum in body of the people in endemic areas of the malaria and presence of asymptomatic variants of the malaria disease in a human body, could make the human body a competitive environment for the SARS-Cov-2, as both diseases may have high binding affinity to ACE2 protein. Malaria endemicity may contribute to lower cases of COVID-19.

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