EXPLORING ANTIVIRAL STRATEGIES AGAINST A BROAD RANGE OF BETA-COVs: SPIKE AND POLYMERASE PROTEINS AS PROMISING ANTI-COV TARGETS.

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Introduction

Since December 2019, over 30 000 000 cases of COVID-19 and 1 million deaths have been reported by WHO. 1 Currently, there are no prophylactic or therapeutic agents specific for SARS-CoV-2 infection. 2

Giving the enormous impact of the COVID-19 pandemic on society and economy and on human health and well-being, there is an urgent need for new antiviral therapies.

The important role that Spike (S) and Polymerase (Pol) proteins have in viral infection and pathogenesis highlights their promising role as potential anti-CoV targets.

Objective: explore conserved druggable regions in SARS-CoV-2 S and Pol protein structures and identify druggable hot spots for the development of new therapies against beta-CoVs (SARS-CoV-2, SARS-CoV and MERS-CoV).

Materials and Methods

Sequence datasets: 1,065 (S) and 1106 (Pol) sequences (SARS-CoV-2, SARS-CoV and MERS-CoV) from all continents, retrieved from public databases.

Amino acid (aa) conservation was calculated and druggability was predicted using computational methods. 3 - 6

Results and Discussion

SPIKE (S)

S1 subunit exhibits higher conservation (99.8%) when compared to S2 (95.6%) in SARS-CoV-2. But, in SARS-CoV and MERS-CoV, S2 presents an higher conservation.

327 residues were ranked with the maximum druggability score in both monomeric and tetrameric conformations of SARS-CoV-2 Pol.

Fingers subdomain (aa 398-580; 627-686) - which is highly conserved across SARS-CoV-2, SARS-CoV and MERS-CoV - is the most promising region.

This subdomain is close to the putative binding site of remdesivir.

We identified 181 new potential hot spot residues for the human SARS-CoV-2 and 72 new hot spot residues for the SARS-CoV, SARS-CoV-2 and MERS-CoV S protein.

S1-RBD and SD1 and S2-CR -HR1 and -CH domains are the most promising druggable S regions.

POLYMERASE (Pol)

We discovered 15 consensus druggable pockets, that can act as antiviral targets for the development of new therapeutic strategies against SARS-CoV-2.

Conclusions

Potential binding pockets can be found in highly conserved regions either in SARS-CoV-2, SARS-CoV and MERS-CoV S and Pol proteins, underpinning their promising role as antiviral targets.

The disclosed hot spots represent attractive targets for structure-function studies and pharmacological modulation.

This study lays the basis for structure-based design of antiviral molecules against a broad spectrum of Beta-CoV.

References

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