Biochemical analysis and review of the active site evolution of SARS-CoV-2 and other coronaviruses.

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Coronaviruses have been a source of significant risk to global health. Almost four million lives have been lost to SARS-CoV-2 (COVID-19). Major efforts are ongoing to mitigate the current pandemic and future outbreaks by designing broad-spectrum drugs to target coronaviruses across species. We identified the positions of residues that participate in binding by using the 3D visualization tool Mol* (https://molstar.org/) to view known inhibitors interacting with the active site of SARS-CoV-2 proteases, two essential enzymes to virus maturation. Experimental structures from the Protein Data Bank (PDB) were used where available and additional models were generated using Robetta (https://robetta.bakerlab.org/). Sequences for additional coronaviridae proteases were obtained from NCBI (https://blast.ncbi.nlm.nih.gov/Blast.cgi). A sequence-based comparison was performed using Clustal (https://www.ebi.ac.uk/Tools/msa/clustalo/) and a structure-based comparison was performed using Dali (http://ekhidna2.biocenter.helsinki.fi/dali/), both using SARS-CoV-2 as the template. The preliminary results show some positions with mutations that remain within the same amino acid classification, groupings by structural, chemical, and functional similarity. Other mutations result in a different classification in that position that may result in a significant impact to the active site structure and binding. We will continue to analyze these changes to identify patterns in the mutations and to identify which mutations have the most impact and are most relevant to potential viral evasion of broad-spectrum drugs.