differs from that in SARS-CoV in the five residues critical for ACE2 binding, namely Y455L, E484K, N493Q, D494S and T501N[52] (FIG. 3b.c). Owing to these residue changes, interaction of SARS-CoV-2 with its receptor stabilizes the two virus-binding hotspots on the surface of hACE2 (REF. [50])[Fig. 30]. Moreover, a four-residue motif in the RBM of SARS-CoV-2 (amino acids 482–485, G-V-E-G) results in a more compact conformation of its hACE2-binding ridge in SARS-CoV and enables better contact with the N-terminal helix of hACE2 (REF. [50]). Biochemical data confirmed that the structural features of the SARS-CoV-2 RBD has strengthened its hACE2 binding affinity compared with that of SARS-CoV[50,52,53].

Similarly to other coronaviruses, SARS-CoV-2 needs proteolytic processing of the S protein to activate the endocytic route. It has been shown that host proteases participate in the cleavage of the S protein and activate the entry of SARS-CoV-2, including transmembrane protease serine protease 2 (TMPRSS2), cathepsin L and furin[47,54,55]. Single-cell RNA sequencing data showed that TMPRSS2 is highly expressed in several tissues and body sites and is co-expressed with ACE2 in nasal epithelial cells, lungs and bronchial branches, which explains some of the tissue tropism of SARS-CoV-2 (REFS [56,57]). SARS-CoV-2 pseudovirus entry assays revealed that TMPRSS2 and cathepsin L have cumulative effects with furin on activating virus entry[53]. Analysis of the cryo-electron microscopy structure of the SARS-CoV-2 S protein revealed that its RBD is mostly in an up conformation, whereas the SARS-CoV S protein assumes equally standing-up and lying-down conformations state[50,51,58,59]. A lying-down conformation of the S protein may be less likely in favor of receptor binding but is helpful for immune evasion[55].