# *Protein-Protein Interactions (PPIs) regulation in CDK1/Cyclin-B and SARS-COV-2-SPIKE/ACE2*

**Abstract**:

Here we discuss the regulation of protein-protein interactions (PPIs) in two protein complex systems: CDK1/Cyclin-B and SARS-CoV-2-RBD/ACE2 which are implicated in the G2/M phase transition of the cell cycle and entry of SARS-CoV-2 virus inside human cell respectively. Previously, it has been thought that CDK/Cyclin binding is not regulated. However, our recent biochemical and computational study showed that CDK1/Cyclin-B binding is regulated through acetylation post-translational modification at active site lysine. Our molecular dynamics simulation (MD) study of the CDK1/Cyclin-B/ATP complex had shown that acetylation perturbed the CDK1/Cyclin-B interface and slightly reduces the ATP binding which is supported by experimental study. Here we extend our previous computational study to uncomplexed CDK1 (unbound to cyclin B) to understand the impact of acetylation on CDK1 structure, dynamics, and energetics upon acetylation and thereby the molecular mechanism by which it can impact the ATP and Cyclin-B binding. Using multiple molecular dynamics (MD) simulations (a cumulated length of a total of 20 $\mu$s) we show that the ATP binding is relatively more favorable in WT than K33AC and K33Q (acetyllysine mimic) both enthalpically and entropically. The active site water molecules play a critical role where they enthalpically stabilize ATP binding relatively more in WT than K33AC and K33Q. Entropic decomposition per residue shows that the big changes upon ATP binding are not from the ATP binding site but from the distant region away from ATP. Our result further suggests that the acetylation/perturbation at the active site region of CDK1 can regulate three PPIs. In SARS-CoV-2-RBD/ACE2 we will show some initial work towards designing SBP1 (a helical segment from ACE2 interfacing RBD) based helical peptide for targeting RBD/ACE2 interaction to block the SARS-CoV-2 entry.