Allosteric regulation of multiple protein-protein interactions in CDK1 enzyme

Protein-protein interactions (PPIs) are gaining recognition as promising therapeutic targets for a wide range of diseases[1–3]. Understanding the mechanisms that regulate PPIs is crucial for designing drugs that can effectively modulate these interactions. Our focus is on unraveling the regulatory processes governing PPIs in protein kinases, a super family of enzymes that regulate numerous biological processes through phosphorylation[4] , a type of post-translational modification. It has been found that the active sites of certain protein kinases are allosterically linked to PPI interfaces[5]. We aim to investigate the connections between PPI interfaces and different regions within protein kinases. In this study, we selected CDK1, a protein kinase involved in cell cycle regulation[6], as a representative model to explore PPI regulation. We used molecular dynamics simulations to investigate how perturbations in the active site of CDK1 modulates PPIs interfaces. Our findings reveal that the active site of CDK1 is coupled to three allosteric regions, which turn out to be three distinct PPIs.

References:

1. Scott, D. E., Bayly, A. R., Abell, C. & Skidmore, J. Small molecules, big targets: Drug discovery faces the protein-protein interaction challenge. *Nat. Rev. Drug Discov.* **15**, 533–550 (2016).

2. Wells, J. A. & McClendon, C. L. Reaching for high-hanging fruit in drug discovery at protein-protein interfaces. *Nature* **450**, 1001–1009 (2007).

3. Ryan, D. P. & Matthews, J. M. Protein – protein interactions in human disease. *Curr. Opin. Struct. Biol.* **15**, 441–446 (2005).

4. Cheng, H. C., Qi, R. Z., Paudel, H. & Zhu, H. J. Regulation and function of protein kinases and phosphatases. *Enzyme Res.* **2011**, 7–9 (2011).

5. Leroux, A. E. & Biondi, R. M. Renaissance of Allostery to Disrupt Protein Kinase Interactions. *Trends Biochem. Sci.* **45**, 27–41 (2020).

6. Brown, N. R. *et al.* CDK1 structures reveal conserved and unique features of the essential cell cycle CDK. *Nat. Commun.* **6**, 1–12 (2015).