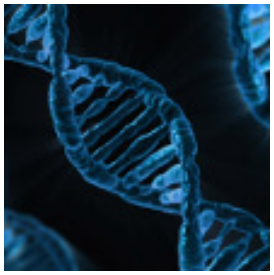

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How do buried residues get phosphorylated?

Protein phosphorylation is the most common post-translation modification of proteins and regulates many biological processes. As a biologically important example we have studied the complex formed by cyclins and cyclin-dependent kinases (CDKs), which play an essential role in the control of the eukaryotic cell cycle. p27 is a protein that binds to and prevents the activation of different G1 and S phase cyclin-CDK complexes. Three sequential phosphorylation events on specific residues of p27, regulate the activity of these complexes and ultimately control cell cycle proliferation or arrest. Notably, the first two post-translational modifications, which are required for the initial activation of these complexes, occur on solvent inaccessible (i.e., buried) tyrosine residues. If these residues are inaccessible to kinases, how do they get phosphorylated then?
We hypothesize that a dynamic equilibrium between the dominant buried state and an transiently open, kinase-accessible state is present in the p27-cyclin A-CDK2 complex, and aim to test this hypothesis through the use of unbiased molecular dynamics and metadynamics simulations. From these simulations we aim to obtain a more detailed understanding of the conformational ensemble of this complex and the binding and release mechanism of p27, as well as to be able to calculate the free energy difference between the bound and unbound states. The latter should prove important in understanding whether the functionally important, but transiently populated state, where Tyr88 of p27 is solvent accessible, is likely to occur spontaneously or not.
More generally, bioinformatics analyses have shown that ˜15% of all phosphorylated residues are buried in the non-phosphorylated state, suggesting that transient exposure might be a general mechanism involved in protein regulation. Thus, our work could open up for a novel and detailed understanding of the structural and dynamical changes involved in a much larger set of proteins.

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