Understanding hypertension at the molecular level via multiscale simulations

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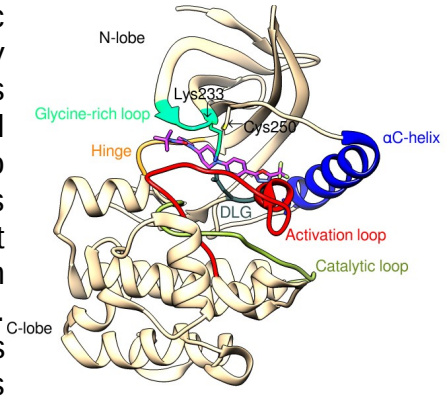
Hypertension is a common chronic disorder that leads to stroke, myocardial infarction, renal failure, and congestive heart failure. Genetic approaches have demonstrated that mutation in many genes regulate renal salt reabsorption and causes variation in the blood pressure. The discovery of renal With No Lysine kinase (WNK) offers a new insight into the sodium, potassium, and blood pressure regulations and body fluid homeostasis. It has been found that mutations in WNK lead to Pseudohypoaldosteronism type II (PHAII), also known as Gordons syndrome. Autophosphorylation at Ser^{382} of activation loop makes WNK1 kinase active. Herein, via molecular dynamics simulations, the effect of phosphorylation on the structure and dynamics of the kinase in the unphosphorylated (uWNK) and phosphorylated (pWNK) complexes with its ligand (WNK463) were studied.



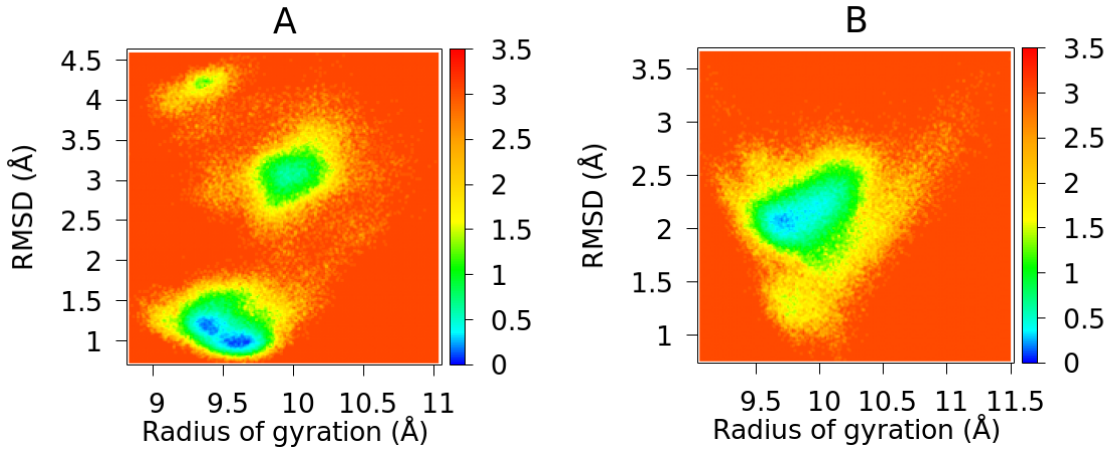


Fig 1: Free energy landscape as a function of C_α RMSD of activation loop and its radius of gyration (R_g) from the MD simulations of uWNK (A) and pWNK (B)

Our simulations reveal that the phosphorylation at Ser^{382} significantly stabilizes the highly flexible activation loop. The pattern of the basin on free energy landscape shows multiple dispersed basin in uWNK and a broader and stable global minimum in pWNK. This suggests the structural disparity among the complexes and uWNK has no preferred conformation selection compare to pWNK.

Next, we have investigated the binding of the inhibitor WNK463 to the kinase (uWNK and pWNK) using the MM-PBSA scheme. The result is shown in figure 2. We have observed a slight favored binding free energy in pWNK compared to uWNK due to lesser unfavorable desolvation polar energy and entropy contributions. In both cases, the binding is favored by the intermolecular electrostatics interactions and van der Waals interactions. The nonpolar component of the solvation free energy also favors the complex formation. However, the polar solvation free energy and the configurational entropy always disfavor the complex formation. It is also to be noted here that the sum of the electrostatics energy and polar

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solvation free energy is postive implying that the favorable electrostatic interaction is overcompensated by the unfavorable polar solvation free energy. Therefore, the complex formation is mainly drived by the van der Waals interactions.

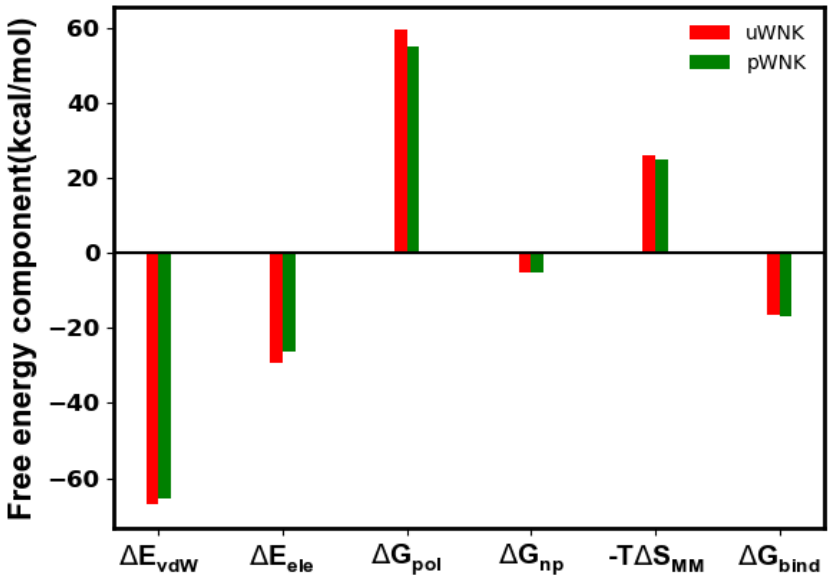

Figure 2: Contributions of different forces to the total binding free energy of WNK463 to pWNK and uWNK.

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