Phosphorylation of Tyrosine 841 Strongly Affects JAK3 Kinase's Activation

Shengjie Sun[1], Lin Li[1,2]

[1] *Computational Science Program, The University of Texas at El Paso, 500 W University Ave, TX, 79968, USA*

[2] *Department of Physics, The University of Texas at El Paso, 500 W University Ave, TX, 79968, USA*

Abstract

Janus Kinase 3 (JAK3) plays a key role in the proliferation, development, and differentiation of various cells. It regulates gene expression by phosphorylation of Signal Transducer and Activators of Transcriptions (STATs). A new JAK3 kinase domain phosphorylation site was found, tyrosine-841 (Y841). The effects of phosphorylated tyrosine-841 (pY841) on ATP/ADP binding affinities of the JAK3 kinase domain were systematically studied and reported here. With the support of TACC, we applied long all-atom molecular dynamic simulations to study the effects of phosphorylation on Y841. The results show that pY841 reduces the size of the cleft between the N-lobe and C-lobe of the JAK3 kinase domain. However, when an ATP/ADP is bound to the kinase pY841 was found to enlarge the cleft. Additionally, for unphosphorylated JAK3 (JAK3-Y841), the binding forces between the kinase domain and ATP or ADP are similar. After phosphorylation of Y841, JAK3-pY841 exhibits more salt bridges and hydrogen bonds between ATP and kinase than ADP and kinase. Consequently, the electrostatic binding force between ATP and kinase is higher than that between ADP and kinase. The result is that compared to ADP, ATP is more attractive to JAK3 when Y841 is phosphorylated. Therefore, JAK3-pY841 tends to bind ATP rather than ADP.

Molecular Dynamic Simulation

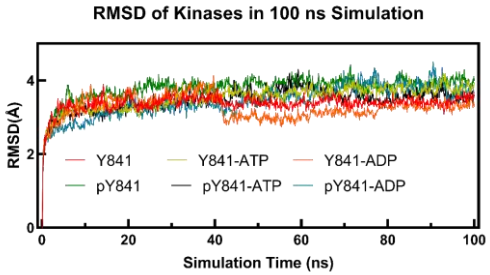

Figure S1: RMSD of the kinase Y841, pY841, and that with ADP or ATP.

Topological and Electrostatic Analysis

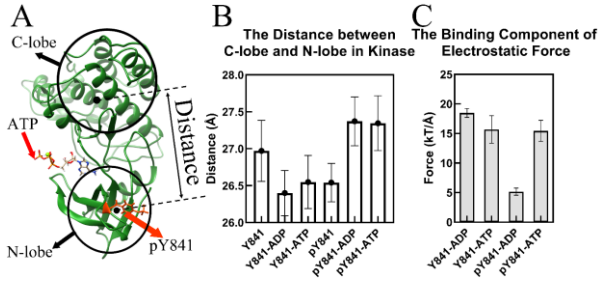

Figure 1: Phosphorylation of JH1-Y841 promotes an activated kinase domain state. A. Ribbon diagram of the JAK3 JH1-pY841 domain with ATP. The JH1 cleft is the space between the N-lobe and C-lobe. B. The distance between the JH1 C-lobe and N-lobe in the simulation of JH1-Y841, JH1-pY841, ATP-JH1-Y841, ATP-JH1-pY841, ADP-JH1-Y841, ADP-JH1-pY841 C. The binding component of the electrostatic force between the JH1 domain (Y841/pY841) and ADP/ATP.

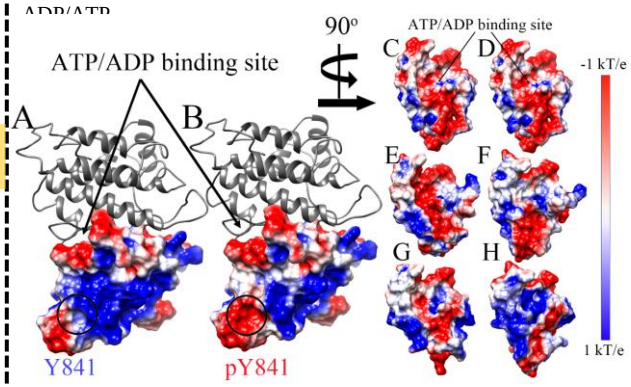

Figure 2: The electrostatic surface of the N-lobe of JAK3 JH before and after simulations. AC. JH1-Y841 before simulations. BD. JH1-pY841 before simulations. E. ATP-JH1-Y841 after 100 ns simulation. F. ATP-JH1-pY841 after 100 ns simulation. G. ADP-JH1-Y841 after 100 ns simulation. H. ADP-JH1-pY841 after 100 ns simulation.

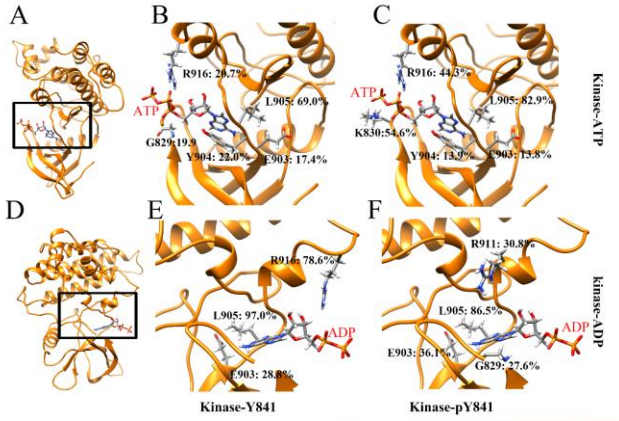

Figure 3: The ribbon diagram of high-occupancy (>10%) hydrogen bonds in A. JH1 bound to ATP. D. JH1 bound to ADP. And hydrogen bonds between residues and nucleotides between B. JH1-Y841-ATP. C. JH1-pY841-ATP. E. JH1-Y841-ADP. F. JH1-pY841-ADP.

Conclusion

- Phosphorylation of Y841 contributed to more salt bridges and hydrogen bonds between ATP and kinase than ADP and kinase.
- The electrostatic binding force between ATP and kinase-pY841 is higher than that between ADP and kinase-pY841.
- ATP is more attractive to JAK3 while ADP is less attractive to JAK3 kinase when Y841 is phosphorylated.

Acknowledgment

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