Exploring the flexibility of Pin1 peptidyl-prolyl isomerase using molecular dynamics simulations

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Pin1 is a peptidyl-proplyl isomerase (PPiase) that catalyses the cis/trans isomerization of the phosphorylated Serine/Threonine-Proline *(pS/T-P)* motifs[1]. Pin1 is involved in many biological processes and the perturbation of its expression level has been implicated in several diseases and different types of cancer. In this manner, Pin1 appears as a therapeutic target in cancer treatment. The main features of Pin1 consist of two distinct domains connected by a flexible linker, the N-terminal WW domain and C-terminal PPiase domain. Both domains are known to bind the pS/T-P motifs but only the PPiase domain acts as a catalytic binder.

Several studies promoted the understanding of how Pin1 exerts its catalytic activity and emphasized the importance of Pin1 domains communication in its activity[2-3]. However, the mechanism for the interdomain communication is still unclear. Hence, here we present a computational study to evaluate the dynamics of Pin1 structural features, taking into account the solvent environment and the conformational changes of the cis/trans proline residue.

Despite the suggesting evidences of some form of interdomain communication, the linker between the WW and PPIase domains has never been crystallized due to its high flexibility. In our present work, we carried out homology modeling to complete the linker, followed by molecular dynamics simulations in the apo form and in the presence of known inhibitors. Additionally, to complete conventional molecular dynamics methods, dynamics important sampling has been performed to investigate the ligand transition from one domain to the other.

Furthermore, by combining the data from solution-phase NMR and computational ensembles we aim to better understand the dynamic side of crucial interactions within the two domains. Explicit comparison with experimental data will thus provide a more complete atomistic picture of the whole Pin1 leading to the optimization of known inhibitors and the design of new inhibitors.

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