World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:19, No:02, 2025

Computational Insights Into Allosteric Regulation of Lyn Protein Kinase: Structural Dynamics and Impacts of Cancer-Related Mutations

Authors : Mina Rabipour, Elena Pallaske, Floyd Hassenrück, Rocio Rebollido-Rios

Abstract : Protein tyrosine kinases, including Lyn kinase of the Src family kinases (SFK), regulate cell proliferation, survival, and differentiation. Lyn kinase has been implicated in various cancers, positioning it as a promising therapeutic target. However, the conserved ATP-binding pocket across SFKs makes developing selective inhibitors challenging. This study aims to address this limitation by exploring the potential for allosteric modulation of Lyn kinase, focusing on how its structural dynamics and specific oncogenic mutations impact its conformation and function. To achieve this, we combined homology modeling, molecular dynamics simulations, and data science techniques to conduct microsecond-length simulations. Our approach allowed a detailed investigation into the interplay between Lyn's catalytic and regulatory domains, identifying key conformational states involved in allosteric regulation. Additionally, we evaluated the structural effects of Dasatinib, a competitive inhibitor, and ATP binding on Lyn active conformation. Notably, our simulations show that cancer-related mutations, specifically I364L/N and E290D/K, shift Lyn toward an inactive conformation, contrasting with the active state of the wild-type protein. This may suggest how these mutations contribute to aberrant signaling in cancer cells. We conducted a dynamical network analysis to assess residue-residue interactions and the impact of mutations on the Lyn intramolecular network. This revealed significant disruptions due to mutations, especially in regions distant from the ATP-binding site. These disruptions suggest potential allosteric sites as therapeutic targets, offering an alternative strategy for Lyn inhibition with higher specificity and fewer off-target effects compared to ATP-competitive inhibitors. Our findings provide insights into Lyn kinase regulation and highlight allosteric sites as avenues for selective drug development. Targeting these sites may modulate Lyn activity in cancer cells, reducing toxicity and improving outcomes. Furthermore, our computational strategy offers a scalable approach for analyzing other SFK members or kinases with similar properties, facilitating the discovery of selective allosteric modulators and contributing to precise cancer therapies.

Keywords : lyn tyrosine kinase, mutation analysis, conformational changes, dynamic network analysis, allosteric modulation, targeted inhibition
Conference Title : ICCB 2025 : International Conference on Cancer Bioinformatics
Conference Location : Amsterdam, Netherlands
Conference Dates : February 03-04, 2025