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Curtailing Thrombosis, the way forward-Deciphering the anti-thrombotic activity of Benzamidine, a small molecule inhibitor of activated Hageman Factor (FXIIa)

Abstract
Background/Aim: Thrombosis occurs when blood clots and blocks a blood vessel thereby reducing blood flow, serving as the underlying mechanism of some globally prominent 'lethal' diseases such as myocardial infarction, ischemic stroke, and venous thromboembolism (VTE). Moreover, the critical roles of activated Hageman Factor XII (FXIIa) in the coagulation cascade have presented it as a viable target for the development of highly effective anti-thrombotics. Benzamidine is a small molecule antagonist recently developed to non-covalently inhibit human plasma β-FXIIa. However, structural and molecular events that account for its potent inhibitory activity remain unresolved, insights that could possibly pave way for the design of novel small-molecule anti-thrombotics.
Methods/Results: Advanced molecular bio-computation and molecular modelling techniques were employed to unravel the mechanistic events that mediate the favorable inhibitory activities of benzamidine. Results revealed that benzamidine disoriented the entire conformation of FXIIa via favorable high-affinity binding, as evidenced by decreased structural compactness and increased structural fluctuation. These alterations in FXIIa structure in turn perturbed active site loops which play crucial roles and enhance pro-coagulation interactions with biological substrates and cofactors, altogether resulting in the consequential inactivation of FXIIa.
Conclusion: Findings provide essential structural and molecular insights that could facilitate the structure-based design of novel antithrombotic compounds with enhanced inhibitory activities.
HPC CONTENT
The lengau cluster CHPC was employed to perform the molecular dynamics (MD) simulations for this study. The openMPI 1.8.8 GNU compilers, the GCC 5.1.0, amber modules and the /apps/chpc/chem/amber/14 application code were integrated to access the Amber14 suite. For system parameterization, the ANTECHAMBER and LEAP modules were incorporated.In analyzing generated MD trajectories, the CPPTRAJ and PTRJ modules were used. Running on 2 nodes and 48 cores, the GPU accelerated PMEMD engine was used.

Presenter Biography

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