Abstract

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Thesis title: **"An investigation to understand the role of key facets involved in the coagulation/anticoagulation process by employing computational and molecular approaches"**

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Hemostasis is an intricate, highly regulated, and specialized process that not only prevents and arrests bleeding/hemorrhage but also eliminates blood clots after the restoration of vascular integrity. The equilibrium between the two processes namely blood coagulation and anticoagulation exclusively depends on a balanced interplay among a series of elements: the coagulation factors (mostly proteolytic enzymes), endothelium, and platelets. Factor VIIa (FVIIa), used in hemophilia treatment, is known to bind to procoagulant receptor Tissue Factor (TF) and initiate coagulation. Recent studies have revealed that FVIIa also binds to EPCR (endothelial protein C receptor), a receptor involved in the protein C/APC-anticoagulant pathway but with unclear hemostatic consequences. Being homologous to protein C, FVIIatoo binds to EPCR through its GLA-domain. Factor Xa (FXa) has a GLA-domain like FVIIa and protein C; however, there is a variation in FVIIa/FXa GLA-domain binding with EPCR in different species such as humans and mice. This thesis work provides detailed insight into differences in species-specific binding of FVIIa GLA-domain and FXa GLA-domain towards EPCR, which may facilitate the designing of FVIIa-mutant molecules for improved therapeutic use associated with bleeding disorders and septic shock. In the next project, we have tried to characterize the dynamics and interactions of cholesterol with the TF-FVIIa-FXa Ternary complex. The effect of cholesterol content and post-translational modifications of TF on TF-FVIIa coagulant activity is still indeterminate. Previous studies suggest that the presence of cholesterol/LDL in atherosclerotic plaques confers high importance to atherogenesis. Aberrant palmitoylation is related to various diseases including neurological disorders like Huntington's disease, Parkinson's disease, Alzheimer's disease, metabolic disorders, and Cancer. Additionally, we also attempted to assess the effect of Palmitoylation, on protein-lipid interactivity in presence of cholesterol. Furthermore, we also undertook a project associated with the virtual screening, docking, and molecular dynamics simulation of antifibrinolytic agents which will prevent blood clot dissolution and abnormal blood loss. Herein, we attempt to find potential antifibrinolytic inhibitors having both maximum specificity and efficacy with minimum side effects. As a part of a collaborative project, an evaluation of in-house synthesized small-molecule inhibitors having potent anti-cancer activity against the programmed death-ligand 1 (PD-L1) was performed using *in silico* approaches.

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