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Topic of Research: Understanding the Implications of Plasma Proteins Modulation by Protein Disulfide Isomerase in Coagulation Mechanism and thrombosis.

Findings

Understanding how Protein Disulfide Isomerase (PDI), thrombin (T), and Antithrombin III (ATIII) regulate coagulation is crucial for grasping their mechanisms and predicting PDI-based interventions' effects on thrombosis. We used in-silico docking to observe PDI's interactions with thrombin, antithrombin, and vitronectin. PDI binds antithrombin via His399 and Gln402, and thrombin via Cys53 and His55 in its kringle domain, while engaging His399, Lys401, and Gln402 near the thrombin's cleavage site. In-vitro, assays showed PDI's ability to control coagulation, especially targeting thrombin-driven fibrin cross-linking. PDI's role in the common pathway, with antithrombin-regulated thrombin, raises questions about its impact on their modulation.

Exploring PDI's role in plasma-mediated thrombus initiation, we screened 167 compounds and identified naringin, quercetin, and QPS as PDI regulators. Naringin induced conformational changes, reducing PDI's activity and coagulation rates. In contrast, QPS enhanced PDI's activity, likely due to sulfate group interactions. In human plasma, these compounds altered APTT and PT, reflecting their coagulation effects.

Blood coagulation assays demonstrated PDI's direct coagulation rate enhancement, further modulated by an activator (QPS) or inhibitor (quercetin). PDI variants (H399R and C53A) revealed their impact on coagulation; arginine enhanced activity via stable disulfide bonds, while C53A exhibited reduced activity. APTT, PT, and TT were affected, notably, TT is more affected. Thrombin reduced PDI activity, restored by the ATIII-fIIa complex, confirmed by SDS-PAGE and western blot, suggesting PDI's utilization of the complex to maintain activity.

In conclusion, our study emphasized PDI's role in coagulation, particularly its modulation of thrombin-dependent pathways. Directly influencing coagulation rates via activators or inhibitors offers therapeutic potential. PDI variants highlighted key amino acid roles. Interplay with thrombin and ATIII underscore PDI's hemostatic importance. By investigating PDI's impact on coagulation rates and its modulation, we gained valuable insights into potential avenues for both prothrombotic and antithrombotic interventions, ultimately contributing to a better understanding of coagulation regulation and thrombosis management.