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**Topic- Protein C Inhibitor interacting role with protein disulfide isomerase in blood coagulation pathways**

Hemostasis is a tightly regulated process that maintains blood fluidity and prevents excessive bleeding. Dysregulation of coagulation or fibrinolysis leads to thrombotic disorders, necessitating alternative therapeutic approaches. Protein C inhibitor (PCI), a serpin family member, inhibits procoagulant and anticoagulant proteins such as thrombin, Factor Xa (FXa), and activated protein C (APC). Protein disulfide isomerase (PDI), a key regulator of thrombosis, modulates platelet accumulation and clot formation

**Findings-** Our study explored the functional role of exosite residues Arg238 and Glu239 in PCI by generating site-directed variants. Structural and functional analyses, including fluorescence spectroscopy, CD spectroscopy, MD simulations, and enzyme inhibition assays, revealed that Glu239 plays a critical role in heparin-dependent inhibition of thrombin, FXa, and APC. We also identified naringin as a PCI activator, enhancing its inhibitory effect on coagulation proteases and modulating clot formation.

To investigate PDI role in hemostasis, we generated histidine and cysteine variants of PDI and analyzed their effects on coagulation assays. Functional studies demonstrated that histidine variants exhibited enhanced procoagulant effects, whereas cysteine variants impaired PDI-mediated clot formation. Protein interaction studies confirmed that PDI selectively interacts with ATIII-thrombin and HCFII-thrombin complexes but not with PCI or its binary complexes. These findings suggest that PDI's regulation of thrombin activity is independent of PCI.

Our study highlights the functional relevance of PCI exosites, the therapeutic potential of naringin, and the selective interaction of PDI with thrombin complexes, providing insights into novel anticoagulant strategies and the mechanistic role of PDI in hemostasis.