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MECHANISMS MEDIATING VASCULAR OCCLUSION IN THROMBOIN FLAMMATORY DISEASES: ROLE OF THIOL ISOMERASES

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Real-time intravital microscopic studies have provided compelling evidence that intravascular cell-cell aggregation directly contributes to vascular occlusion and tissue damage, a leading cause of morbidity and mortality of patients with cardiovascular diseases. In particular, platelet-leukocyte interactions on the activated endothelium are crucial for the initiation and progression of thrombotic and inflammatory diseases. Platelet-leukocyte adhesion is mediated mainly through the interactions of platelet P-selectin and glycoprotein Ibα with neutrophil P-selectin glycoprotein ligand-1 and αMβ2 integrin, respectively. Despite our knowledge of the major receptors and counter-receptors, it remains poorly understood how the receptor-counter-receptor interactions are controlled during cardiovascular diseases. Evidence is mounting that the function of plasma proteins and cell surface receptors involved in thrombosis and inflammation is controlled by oxidation or reduction of allosteric disulfide bonds. Thiol isomerases catalyze thiol-disulfide exchange and regulate protein folding and function. Intriguingly, despite having an endoplasmic reticulum retention signal, several thiol isomerases are released from intravascular cells and detected in the circulation and on the cell surface. We have demonstrated that the plasma level of protein disulfide isomerase (PDI), a prototypic thiol isomerase, is enhanced during thrombosis and vascular inflammation and that extracellular PDI plays a critical role in platelet-leukocyte aggregation under thromboinflammatory conditions. In this presentation, I will discuss the molecular mechanism by which PDI participates in the initiation and progression of thromboinflammatory diseases. A better understanding of the molecular basis of thiol isomerase-mediated cell-cell interactions will provide insights into the development of novel therapeutic agents for the prevention and treatment of cardiovascular diseases.

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