**New Research in Nature Communications Sheds Light on Fibrinogen Biogenesis and Hepatic Fibrinogen Storage Disease**

A pioneering study published in *Nature Communications* on October 26, 2024 (https://www.nature.com/articles/s41467-024-53639-x), reveals critical insights into the regulation of hepatic fibrinogen biogenesis and the formation of pathological inclusions in liver cells. Researchers from the Department of Pharmacology at the University of Virginia School of Medicine have identified the SEL1L-HRD1 protein complex of the endoplasmic reticulum (ER)-associated degradation (ERAD) pathway as a key regulator of hepatic fibrinogen storage disease (HFSD).

HFSD is characterized by the impaired secretion of fibrinogen, an essential blood coagulation factor, leading to the accumulation of fibrinogen-positive inclusion bodies and hypofibrinogenemia. Despite its clinical significance, the molecular dynamics of fibrinogen production within the ER have remained largely unexplored until now.

The research demonstrates that a deficiency in the SEL1L-HRD1 ERAD complex in hepatocytes results in the formation of hepatocellular inclusion bodies, which contain fibrinogen as a major component. Through proteomics and biochemical assays, the study reveals that the degradation of misfolded fibrinogen subunits—Aα, Bβ, and γ chains—by SEL1L-HRD1 ERAD is crucial for forming a functional fibrinogen complex within the ER.

“Our findings underscore the essential role of SEL1L-HRD1 in maintaining proper fibrinogen biogenesis,” said Dr. Shengyi Iris Sun, Associate Professor in the Department of Pharamcology. “By regulating the degradation of misfolded fibrinogen, this complex ensures the proper assembly and secretion of this vital protein.”

In a significant clinical context, the study also highlights how SEL1L-HRD1 ERAD mitigates the pathogenicity of two disease-causing fibrinogen γ mutants, emphasizing its potential as a therapeutic target in protein-misfolding diseases.

This research not only elucidates the mechanisms behind fibrinogen production but also contributes to a broader understanding of protein-misfolding diseases, offering new avenues for therapeutic interventions.