Escaping the Matrix: Identifying ADAMTSL2 as the Trigger for Irreversible Liver Fibrosis Through Protein Modeling

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Liver fibrosis is a global health crisis, affecting approximately 7.3% of adults worldwide. The disease is progressive, with advanced stages characterized by formation of a permanent extracellular matrix (ECM) composed of fibrillin-1 and tropoelastin (TE). The mechanism triggering the transition remains poorly understood. This study investigated the role of ADAMTS-like protein 2 (ADAMTSL2) as a molecular stabilizer of the TE-fibrillin-1 complex enabling irreversible ECM formation. Multiple 3D structural models of ADAMTSL2, fibrillin-1, and TE were reliably generated for the first time using AlphaFold 3. Their conformational stability was validated through molecular dynamics (MD) simulations in GROMACS to ensure structural integrity under hepatic conditions. Protein-protein docking simulations were then performed in HADDOCK3 to characterize the binding interfaces and energetic affinities of the complex. The results provide the first molecular evidence that ADAMTSL2 has strong interactions with specific domains within fibrillin-1. MD trajectories demonstrated that ADAMTSL2 significantly reduces the conformational entropy of fibrillin-1 and energetic scoring in docking analysis revealed that this stabilizing effect creates a kinetically favorable environment for the recruitment and deposition of TE, leading to assembly of insoluble elastic fibers into an ECM. These findings identify ADAMTSL2 as the critical trigger for formation of permanent hepatic ECM and present ADAMTSL2 as a novel therapeutic target for liver fibrosis treatment. After docking over 1600 FDA-approved drugs in the ZINC20 database for inhibition of ADAMTSL2, Elbasvir was identified as a potent inhibitor and shows promise as a candidate therapy to halt progression of liver fibrosis.

Awards Won:

Third Award of $1,200