Targeting CRM1-HMGB1 Nuclear Translocation in Type 2 Diabetes-Driven Metabolic Dysfunction Associated Steatotic Liver Disease

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Abstract
Introduction: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) has a high incidence in Type-2 Diabetes (T2D) as it relates to the evolution of Non-Alcoholic Steatohepatitis (NASH). Acetyl-High Mobility Group Box 1 (HMGB1) is the proinflammatory isoform of HMGB1, a DAMP released in hepatic inflammatory T2D. The nuclear exporter Chromosomal Maintenance 1 (CRM1) maintains the nuclear-cytoplasm cascade of hepatic HMGB1 in T2D. We hypothesize that target inhibition of CRM1/HMGB1 nuclear shuttle in T2D/NASH. Methods: We performed immunohistochemical quantification of Acetyl-HMGB1 and CRM1 in human liver biopsies from control (healthy), T2D, and T2D-NASH (n:4 per group), and H&E evaluated inflammation and disease stratification. We performed targeted inhibition of CRM1 using Leptomycin-B and HMGB1 with Glycyrrhizin in T2D Huh7 human hepatocytes. Results: T2D subjects with NASH exhibit an increase in acetyl-HMGB1 nuclear and cytoplasmic translocation compared to DM and controls. Acetyl-HMGB1 increased 2-fold in the nucleus and 4-fold in the cytoplasm; CRM1 increased 6-fold in the nucleus and 8-fold in the cytoplasm of T2D/NASH subjects compared to controls. Targeted inhibition of CRM1 and HMGB1 prevented acetyl-HMGB1 hepatocyte release with the most prominent effect in T2D-NASH conditions. Conclusions: Targeting hepatic CRM1/HMGB1 inhibition identifies the potential therapeutic targeting of the CRM1/HMGB1 shuttling process in T2D-driven MASLD.

Keywords: Type-2 Diabetes, MASLD, HMGB1, CRM1, Inflammation, Hepatic