

Investigating the Role of TM6SF2 E167K in ER Stress and Unfolded Protein Response Signaling in MASH

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Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) in which excessive lipid accumulation in the liver leads to inflammation and damage to hepatocytes. One key cellular process that may contribute to this progression is endoplasmic reticulum (ER) stress. When hepatocytes experience lipotoxicity, excessive fatty acids disrupt ER homeostasis, leading to activation of the unfolded protein response (UPR). At first, the UPR activates adaptive mechanisms to restore ER homeostasis by increasing protein folding machinery and promoting the degradation of misfolded or damaged proteins. However, persistent lipotoxicity will overwhelm adaptive mechanisms and shift UPR signaling toward pro-apoptotic and pro-inflammatory pathways, contributing to hepatocyte death, fibrosis, and MASH progression.

Previous studies have identified genetic variants in genes such as TM6SF2, PNPLA3, and GCKR that increase susceptibility to MASLD and MASH. However, how these genetic variants alter ER stress responses and UPR signaling remain unknown. We hypothesize that hepatocytes with different genetic backgrounds may respond differently to lipotoxicity-induced ER stress. Specifically, we are testing if **TM6SF2** E167K variant increases hepatocyte susceptibility to lipotoxicity, resulting in greater ER stress and altered UPR signaling. To test this, we will compare ER stress responses and UPR signaling in iPSC-derived hepatocytes carrying the **TM6SF2** E167K variant to a healthy control and CRISPR-corrected isogenic line. We previously observed increased CHOP mRNA expression in a MASH line carrying the TM6SF2 variant, and the corrected isogenic line will help determine whether this difference is specifically caused by the TM6SF2 variant. Gene expression of key UPR signaling will be assessed using qPCR along with protein-level analyses. By determining how **TM6SF2** E167K variant alters ER stress responses during lipotoxicity, our study aims to provide insight into how genetic differences contribute to MASH progression and identify potential therapeutic targets for genetically susceptible patients with MASH.