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Myeloid Endoplasmic Reticulum Resident Chaperone GP96 Facilitates Inflammation and Steatosis in Alcohol-Associated Liver Disease

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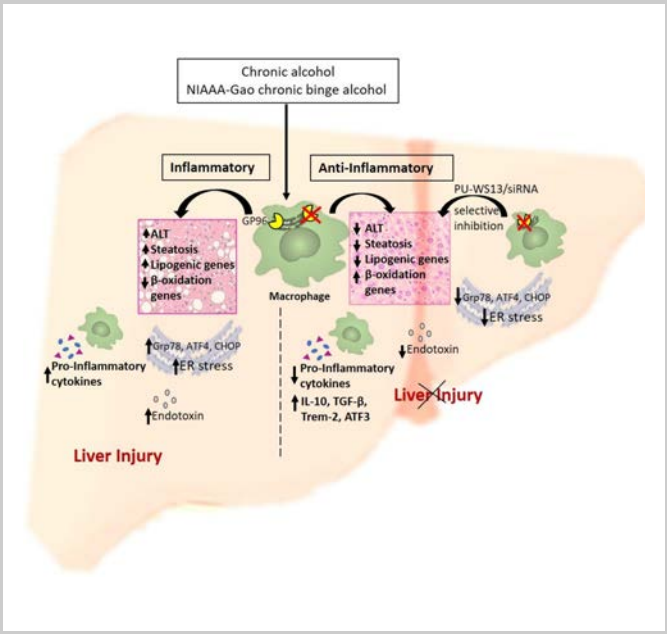

I am a Postdoctoral Associate in Pranoti Mandrekar's Lab in Department of Medicine. I am investigating the role of innate immune cells, TLRs, stress-induced chaperones, and their inhibitors during alcohol-mediated liver injury. I received my PhD from PGIMER, Chandigarh, India. During my PhD, I identified the immunomodulatory efficacy and therapeutic potential of recombinant antigens of *L. donovani* when used as adjunct to the currently used highly toxic drugs using experimental animal model.

Alcohol-related liver disease (ALD) is characterized by steatosis or fatty liver, steatohepatitis and fibrosis which can progress to cirrhosis and hepatocellular carcinoma (HCC). The mechanisms involved in ALD pathogenesis are mainly include acetaldehyde-mediated toxicity, oxidative and endoplasmic reticulum (ER) stress, gut-derived mediators, pro-inflammatory response, and cell death. Currently, there are no FDA-approved therapies for alcoholic hepatitis (AH) and standard of care includes alcohol abstinence, corticosteroids, nutritional therapy, biologics such as anti-TNFa and liver transplantation. Chronic insults including alcohol exposure disturb cellular homeostasis and induce stress-mediated chaperone, known as heat shock proteins (HSPs) in the ER and cytoplasm.

Our lab investigates the role of different HSPs in ALD. Previously, we reported the pathogenic role and therapeutic potential of cytosolic HSP90 in ALD. Glycoprotein 96 (GP96) is an ER paralog of HSP90, a master chaperone required for the folding, processing, and trafficking of several client proteins, including toll-like receptors (TLRs), integrins, Wnt co-receptors and insulin-like growth factors. The role of GP96 has been identified in metabolic diseases and cancer, but its role in ALD remains unknown.

We reported the clinical relevance of GP96/HSP90B1 by showing its significant induction in human AH and murine livers, prominently in macrophages, after chronic alcohol administration. Utilizing cell-specific knock-out mouse model, we found that myeloid-specific deletion of GP96 in mice (M-GP96KO) prevents chronic alcohol-mediated liver injury, steatosis, and inflammation. We found higher expression of anti-inflammatory genes and markers of restorative macrophages in livers of M-GP96KO mice, with alteration in hepatic lipid homeostasis and ER stress. We demonstrate an important role for GP96 in macrophage activation, using a cell permeable specific inhibitor, PU-WS13, and GP96 specific siRNA, markedly reducing pro-inflammatory cytokine production in murine primary macrophages. These findings highlight a novel and critical role for liver macrophage ER resident chaperone GP96 in ALD and its targeted inhibition represents a promising therapeutic approach in ALD.