Chronic liver diseases (CLDs) are characterised by leukocyte infiltration which drives chronic inflammation, fibrosis and cirrhosis. Hepatic sinusoidal endothelial cells (HSEC) play a critical role in liver homeostasis, regulating the immune microenvironment and maintaining tolerance. HSEC line the low shear environment of the hepatic sinusoids in which leukocyte recruitment occurs. They undergo substantial phenotypic changes during CLD, yet how this influences the immune microenvironment in liver disease remains poorly understood. Mannose receptor (MR) and plasmalemma vesicle-associated protein (PLVAP) are atypical adhesion molecules, expressed within specialised vascular beds, although their contribution to CLD remains unknown. We sought to characterise MR and PLVAP expression in normal and diseased human liver tissue and aimed to understand their regulation in primary human HSEC.

Immunohistochemistry studies demonstrated a distinct and mutually exclusive expression pattern, with homogenous MR expression throughout normal liver sinusoids, and PLVAP localisation to peri-venular sinusoids. In CLD, MR expression was lower, displaying disrupted homogeneity, whilst PLVAP was significantly upregulated, correlating spatially and quantitatively with collagen deposition and fibrosis independently of aetiology. Mutual exclusivity and endothelial identity of MR+ and PLVAP+ cells were confirmed by dual immunofluorescence. PLVAP co-localised with endothelial marker, CD31, whilst MR co-localised with sinusoidal marker L-SIGN (liver/lymph node-specific intercellular adhesion molecule-3 grabbing non-integrin). Primary HSEC were isolated from human liver tissue by immunomagnetic selection and MR/PLVAP expression was confirmed by immunofluorescence, allowing regulation studies to be conducted using these cells. Notably, whilst most HSEC were MR-positive, a subset of cells expressed PLVAP, recapitulating observations in situ within human liver. A high-content imaging assay was designed to investigate MR/PLVAP expression in response to various treatment conditions in a high-throughput manner. Contradictory to previous findings, MR levels did not fluctuate following pro-inflammatory stimulation (TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; LPS, lipopolysaccharide), suggesting a distinct MR regulation mechanism within HSEC. Contrastingly, PLVAP expression increased following TNF-α and IL-1β treatment, and was significantly upregulated in the presence of VEGF (vascular endothelial growth factor), confirming previous reports.

In conclusion, these data define two sinusoidal endothelial cell subsets, characterised by reciprocal MR/PLVAP expression, which may have distinct roles in homeostasis and inflammation. Furthermore, MR and PLVAP are differentially regulated within HSEC in vitro, with PLVAP being increased by pro-inflammatory stimuli and growth factors, supporting its upregulation in CLD. Targeting HSEC, with the aim of reprogramming the balance between MR and PLVAP expression, may represent a novel therapeutic approach in CLD.