Phosphatidylserine-Dependent Clearance of Damaged Red Blood Cells by Liver Sinusoidal Endothelial Cells in Alcohol-Related Liver Disease

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Abstract

Alcohol-related liver disease (ALD) and ALD-related mortality are associated with hemolysis, increased erythrophagocytosis, and disturbed iron homeostasis. While macrophage-mediated erythrophagocytosis is well established, we investigated the contribution of liver sinusoidal endothelial cells (LSECs) to handling oxidatively damaged or ethanol-primed red blood cells (RBCs) in ALD. Live-cell imaging demonstrated that damaged RBCs were rapidly taken up by SK-HEP1 cells, an endothelial cell line with LSEC-like characteristics, and RBC uptake was associated with induction of heme oxygenase-1 (HO-1) and activation of its upstream regulator Nrf2. siRNA-mediated knockdown of the scavenger receptor Stabilin-1 attenuated RBC-induced HO-1 expression, supporting a role for Stabilin-1 in efferocytic signaling. Exposure of RBCs to ethanol concentrations as low as 25 mM induced phosphatidylserine externalization and rendered erythrocytes efferocytosis-competent. Lysed RBCs and free hemin elicited comparable oxidative stress responses. In murine models of hemolysis and chronic ethanol feeding, hemoglobin-derived signals were detected within sinusoidal structures showing a diffuse CD206-positive distribution pattern consistent with the sinusoidal scavenger compartment. Similar signals were observed in sinusoidal endothelial regions in human heavy drinkers with clinical signs of hemolysis. Together, these data suggest that LSECs may represent an additional component of RBC clearance in ALD, alongside macrophages and hepatocytes, with implications for hepatic iron handling.