Direct Ingestion of Oxidized Red Blood Cells (Efferocytosis) by Hepatocytes.

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Abstract

PURPOSE: Both hepatic iron accumulation and hemolysis have been identified as independent prognostic factor in alcohol-related liver disease (ALD); however, the mechanisms still remain poorly understood. We here demonstrate that hepatocytes are able to directly ingest aged and ethanol-primed red blood cells (RBCs), a process termed efferocytosis. METHODS: Efferocytosis of RBCs was directly studied in vitro and observed by live microscopy for real-time visualization. RBCs pretreated with either CuSO(4) or ethanol following co-incubation with Huh7 cells and murine primary hepatocytes. Heme oxygenase-1 (HO-1) and other targets were measured by q-PCR. RESULTS: As shown by live microscopy, oxidized RBCs, but not intact RBCs, are rapidly ingested by both Huh7 cells and murine primary hepatocytes within 10 minutes. In some cases, more than 10 RBCs were seen within hepatocytes, surrounding the nucleus. RBC efferocytosis also rapidly induces HO1, its upstream regulator Nuclear factor erythroid 2-related factor 2 (Nrf2) and ferritin, indicating efficient heme degradation. Preliminary data further suggest that hepatocyte efferocytosis of oxidized RBCs is, at least in part, mediated by scavenging receptors such as ASGPR1. Of note, pretreatment of RBCs with ethanol but also heme and bilirubin also initiated efferocytosis. In a cohort of heavy human drinkers, a significant correlation of hepatic ASGPR1 with the heme degradation pathway was observed. CONCLUSION: We here demonstrate that hepatocytes can directly ingest and degrade oxidized RBCs through efferocytosis, a process that can be also triggered by ethanol, heme and bilirubin. Our findings are highly suggestive for a novel mechanism of hepatic iron overload in ALD patients.