Patients With Acute-on-Chronic Liver Failure Have Increased Numbers of Regulatory Immune Cells Expressing the Receptor Tyrosine Kinase MERTK

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BACKGROUND & AIMS
Characteristics of decompensated cirrhosis and acute-on-chronic liver failure (ACLF) include susceptibility to infection, immuneparesis, and monocyte dysfunction. MER receptor tyrosine kinase (MERTK) is expressed by monocytes and macrophages and contributes to down-regulation of innate immune responses. We investigated whether MERTK expression is altered on monocytes from patients with liver failure.

METHODS
We analyzed blood and liver samples collected from patients admitted to the liver intensive therapy unit at King's College Hospital in London from December 2012 through July 2014. Patients had either ACLF (n = 41), acute decompensation of cirrhosis without ACLF (n = 9), cirrhosis without decompensation (n = 17), or acute liver failure (n = 23). We also analyzed samples from healthy individuals (controls, n = 29). We used flow cytometry to determine the level of innate immune function, and associated the findings with disease severity. We developed an assay to measure recruitment and migration of immune cells from the tissue parenchyma. Immunohistochemistry and confocal microscopy were used to determine levels of MERTK in bone marrow, liver, and lymph node tissues. We performed immunophenotype analyses and measured the production of tumor necrosis factor and interleukin 6 and intracellular killing of Escherichia coli by monocytes and peritoneal macrophages incubated with lipopolysaccharide, with or without an inhibitor of MERTK (UNC569).

RESULTS
The number of monocytes and macrophages that expressed MERTK was greatly increased in the circulation, livers, and lymph nodes of patients with ACLF, compared with patients with stable cirrhosis and controls. MERTK expression (mean fluorescence intensity) correlated with the severity of hepatic and
extrahepatic disease and systemic inflammatory responses. Based on immunophenotype, migration, and functional analyses, MERTK-expressing monocytes migrate across the endothelia to localize into tissue sites and regional lymph nodes. Expression of MERTK reduced the response of cultured monocytes to lipopolysaccharide; the addition of UNC569 restored production of inflammatory cytokines in response to lipopolysaccharide.

CONCLUSIONS
Patients with ACLF have increased numbers of immunoregulatory monocytes and macrophages that express MERTK and suppress the innate immune response to microbes. The number of these cells correlates with disease severity and the inflammatory response. MERTK inhibitors restore production of inflammatory cytokines by immune cells from patients with ACLF, and might be developed to increase the innate immune response in these patients.