Neutrophil Toll-Like Receptor 9 Expression and the Systemic Inflammatory Response in Acetaminophen-Induced Acute Liver Failure


OBJECTIVES
There is a marked propensity for patients with acetaminophen-induced acute liver failure to develop sepsis, which may culminate in multiple organ failure and death. Toll-like receptors sense pathogens and induce inflammatory responses, but whether this is protective or detrimental in acetaminophen-induced acute liver failure remains unknown.

DESIGN, SETTING, AND PATIENTS
We assessed Toll-like receptor expression on circulating neutrophils and their function in 24 patients with acetaminophen-induced acute liver failure and compared with 10 healthy controls.

INTERVENTIONS
Neutrophil Toll-like receptor 2, -4, and -9 expression and cytokine production and function were studied ex vivo at baseline and following stimulation with lipopolysaccharide, oligodeoxynucleotides, ammonium chloride, and interleukin-8. To examine the influence of acetaminophen-induced acute liver failure plasma and endogenous DNA on Toll-like receptors-9 expression, healthy neutrophils were incubated with acetaminophen-induced acute liver failure plasma with and without deoxyribonuclease-I.

MEASUREMENTS AND MAIN RESULTS
Circulating neutrophil Toll-like receptor 9 expression was increased in acetaminophen-induced acute liver failure on day 1 compared with healthy controls (p = 0.0002), whereas Toll-like receptor 4 expression was decreased compared with healthy controls (p < 0.0001). Toll-like receptor 2 expression was unchanged. Neutrophil phagocytic activity was decreased, and spontaneous oxidative burst increased in all patients with acetaminophen-induced acute liver failure compared with healthy controls (p < 0.0001). Neutrophil Toll-like receptor 9 expression correlated with plasma interleukin-8 and peak ammonia concentration (r = 0.6; p < 0.05) and increased with...
severity of hepatic encephalopathy (grade 0-2 vs 3/4) and systemic inflammatory response syndrome score (0-1 vs 2-4) \( (p < 0.05) \). Those patients with advanced hepatic encephalopathy (grade 3/4) or high systemic inflammatory response syndrome score (2-4) on day 1 had higher neutrophil Toll-like receptor 9 expression, arterial ammonia concentration, and plasma interleukin-8 associated with neutrophil exhaustion. Healthy neutrophil Toll-like receptor 9 expression increased upon stimulation with acetaminophen-induced acute liver failure plasma, which was abrogated by preincubation with deoxyribonuclease-I. Intracellular Toll-like receptor 9 was induced by costimulation with interleukin-8 and ammonia.

CONCLUSION
These data point to neutrophil Toll-like receptor 9 expression in acetaminophen-induced acute liver failure being mediated both by circulating endogenous DNA as well as ammonia and interleukin-8 in a synergistic manner inducing systemic inflammation, neutrophil exhaustion, and exacerbating hepatic encephalopathy.