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Forty to sixty percent of children with short bowel syndrome (SBS) experience intestinal failure associated liver disease (IFALD), a major cause of mortality in patients who survive long term with SBS. Steatosis is a key component of the hepatic dysfunction and persists even after weaning from parenteral nutrition. We recently demonstrated accelerated steatosis after 50% small bowel resection (SBR) in mice when compared with unoperated mice under identical conditions. IFALD has been associated with the massive inflammatory cytokine responses seen during recurrent episodes of sepsis in SBS patients. Toll–like receptor 4 (TLR4) is a key regulator of the inflammatory cytokine response seen in these episodes. Further, TLR4 signaling outside of sepsis has been implicated in the development of steatosis in other disease processes such as non-alcoholic fatty liver disease. The purpose of this study was to determine whether TLR4 signaling is critical to the development of resection associated hepatic steatosis.

Male C57BL6 (control) and TLR4-knockout (KO) mice underwent 50% proximal SBR. Liver sections were analyzed to obtain the percent lipid content and Ileal sections were assessed for morphological adaptation. Intestinal TLR4 mRNA expression was measured at 7 days and 10 weeks. Compared to controls, TLR4 KO mice demonstrated similar weight gain and morphological adaptation after SBR. Hepatic steatosis was decreased 32-fold in the absence of TLR4. Intestinal TLR4 mRNA expression was significantly elevated 7 days after SBR. We also found that TLR4 expression in the intestine is 20-fold higher in whole bowel compared with isolated enterocytes.

TLR4 signaling is not required for functional or morphological intestinal adaptation after massive small bowel resection. Conversely, it is critical in the development of resection-associated steatosis. This combination of effects makes TLR4 signaling a potential target for preventing resection-associated hepatic dysfunction without adversely affecting adaptation and thus weaning from parenteral nutrition.