Analysis of Cd14 as a genetic modifier of experimental inflammatory bowel disease (IBD) in mice

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BACKGROUND AND AIM:: By combining QTL and gene expression analyses, we have previously identified Cd14 as a potential candidate gene contributing to the differential IBD susceptibility of C3H/HeJBir (C3/J)-Il10(-/-) mice [carrying IBD-resistance alleles at this QTL (Cdcs6)] and C57BL/6J (B6)-Il10(-/-) mice, corroborating studies that showed an association of a CD14-promoter polymorphism with Crohn's disease and ulcerative colitis. The aim of the present study was to analyze the molecular mechanisms leading to differential intestinal expression of Cd14 and its contribution to IBD development. METHODS:: Intestinal CD14 expression was assessed by FACS, immunohistochemistry, and ELISA on supernatants of primary epithelial cell and tissue cultures. RAW264.7 cells were stimulated with LPS and PGN in the presence or absence of CD14. Cd14 alleles were sequenced and promoters cloned for luciferase assays in transfected RAW264.7 cells. The severity of typhlocolitis between Cd14(-/-) and wild-type mice was compared in 2 distinct mouse models of IBD (acute DSS and Il10(-/-)). RESULTS:: In the gut, CD14 was detected mainly in its soluble form (sCD14), with higher expression in C3/J-Il10(-/-) mice. Polymorphisms in C3/J mice caused higher activity of the Cd14 promoter (luciferase assays). Intestinal sCD14 concentrations influenced the LPS and PGN responses of RAW264.7 cells. In vivo, genetic deletion of Cd14 aggravated colitis in both mouse models of IBD. CONCLUSIONS:: Our study shows that Cd14-promoter polymorphisms affect CD14 expression and confirms the protective effect of CD14 against experimental IBD, potentially mediated by TLR2- and TLR4-dependent effects on intestinal barrier function. These findings support the concept that human CD14-promoter polymorphisms contribute to disease development. Inflamm Bowel Dis 2009.
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