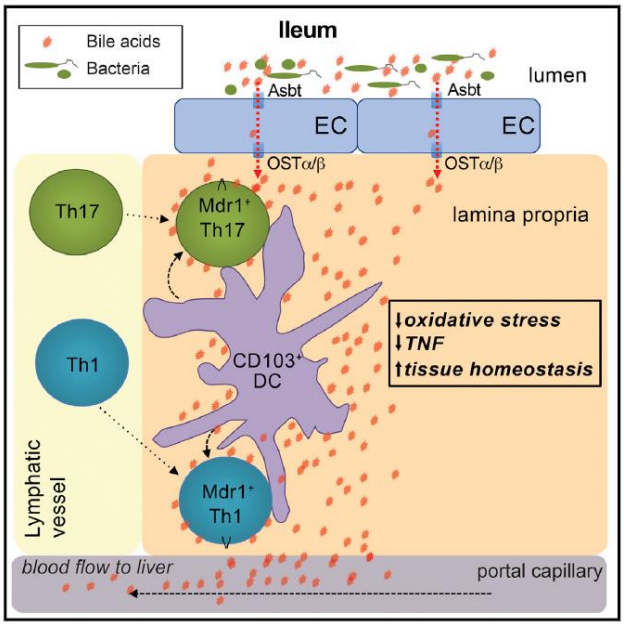
The Xenobiotic Transporter Mdr1 Enforces T Cell Homeostasis in the Presence of Intestinal Bile Acids

CD4+ T cells are tightly regulated by microbiota in the intestine, but whether intestinal T cells interface with host-derived metabolites is less clear. Hisako Kayama, Kiyoshi Takeda and their research group showed that CD4+ T effector (T_{eff}) cells upregulated the xenobiotic transporter, Mdr1, in the ileum to maintain homeostasis in the presence of bile acids. Whereas wild-type T_{eff} cells upregulated Mdr1 in the ileum, those lacking Mdr1 displayed mucosal dysfunction and induced Crohn's disease-like ileitis following transfer into $Rag1^{-/-}$ hosts. Mdr1 mitigated oxidative stress and enforced homeostasis in T_{eff} cells exposed to conjugated bile acids (CBAs), a class of liver-derived emulsifying agents that actively circulate through the ileal mucosa. Blocking ileal CBA reabsorption in transferred $Rag1^{-/-}$ mice restored Mdr1-deficient T_{eff} cell homeostasis and attenuated ileitis. Further, a subset of ileal Crohn's disease patients displayed MDR1 loss of function. Together, these results suggest that coordinated interaction between mucosal T_{eff} cells and CBAs in the ileum regulate intestinal immune homeostasis.



The role of host-derived intestinal metabolites in mucosal immune regulation is poorly understood. The authors show that effector CD4+ T cells upregulate expression of the xenobiotic transporter, Mdr1, in the ileum to safeguard immune homeostasis, revealing an important immunologic consequence of ileal bile acid reabsorption.

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