IBD

Novel mechanism for hepatic complications in IBD

Vascular adhesion protein 1 (VAP1), an ectozone with amine oxidase activity, is implicated in the induction of mucosal addressin cell adhesion molecule 1 (MAdCAM1) expression, according to a study published in *Hepatology*. This induction represents a novel mechanism by which inflammation and thus hepatic complications occur in patients with IBD.

“T cells originally activated in the gut are recruited to the liver in patients with primary sclerosing cholangitis as a consequence of aberrant MAdCAM1 expression,” explains the study’s corresponding author David H. Adams (University of Birmingham, UK). However, until now the mechanism underlying the expression of MAdCAM1 (which is characteristic of IBD) in the liver was unclear.

As VAP1 is present in the liver and in inflamed gut the researchers investigated whether VAP1 could induce MAdCAM1 expression in *in vitro* experiments with human cells and *in vivo* experiments in mice. Populations of hepatic endothelial cells were incubated with methylamine (a substrate of VAP1) or a combination of methylamine and tumor necrosis factor (TNF). The authors used lymphocyte adhesion assays to determine that the

induced MAdCAM1 was functional. To confirm their findings, the authors treated cultures of human liver tissue slices with methylamine, which resulted in expression of MAdCAM1 that was dependent on VAP1.

“Because methylamine is a natural VAP1 substrate found in food, wine and cigarette smoke we wanted to see if it could induce MAdCAM1 expression *in vivo*,” says Adams. Mice fed with methylamine showed increased MAdCAM1 expression, which confirms that VAP1 substrates given orally can induce MAdCAM1 expression.

The authors suggest that an increased amount of methylamine enters the liver of patients with IBD because of enhanced absorption of food or wine via the inflamed gut, or from cigarette smoke, where it acts as a substrate for VAP1 on hepatic endothelium. Such an effect can lead to further increases in the expression of MAdCAM1, which then promotes the recruitment of mucosal effector cells. This recruitment can cause tissue damage, which could result in two frequent complications of IBD—primary sclerosing cholangitis and autoimmune hepatitis. Targeting VAP1 could downregulate MAdCAM1 expression, which would

Human hepatic endothelial cells express high levels of the gut homing receptor MAdCAM1 (red) in response to treatment with methylamine and TNF. Courtesy of D. H. Adams.

lead to resolution of both liver and gut inflammation.

“This study supports the use of VAP1 enzyme inhibitors to treat patients with primary sclerosing cholangitis,” concludes Adams. “These inhibitors are currently being developed and we hope to move into clinical trials with them in the near future.”

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Original article Liaskou, E. et al. Regulation of MAdCAM-1 expression in human hepatic endothelium by VAP-1 amine oxidase activity. *Hepatology* doi:10.1002/hep.24085