CLOSTRIDIUM DIFFICILE

Hypoxia-inducible factor protects intestinal mucosa from *Clostridium difficile* induced injury

Hypoxia-inducible factor (HIF) signaling protects the intestinal mucosa from injury induced by *Clostridium difficile* toxins, according to the results of a study published in *Gastroenterology*.

C. difficile toxins induce intestinal injury by disrupting the intestinal epithelial barrier. Innate host response mechanisms are currently not well understood. "In the intestinal mucosa, activation of the HIF1 complex leads to the production of factors that aid in the maintenance of barrier function, including intestinal trefoil factor, CD73 and MUC3," explains Simon Hirota, one of the authors of the study. "Given the importance of this pathway in the maintenance of barrier function, we hypothesized that mucosal induction of HIF1 signaling was an innate response to *C. difficile* [infection] and that the downstream production of protective factors could afford barrier protection in *C. difficile*-associated disease."

To test their hypothesis, Hirota and colleagues assessed messenger RNA and protein levels of HIF1α in human mucosal biopsy samples from patients with *C. difficile*-associated disease and in healthy samples exposed to *C. difficile* toxins. In addition, *C. difficile* toxins were introduced into mice with deletion of HIF1α in the intestinal epithelium.

> "...Improving HIF1 activity could represent a novel approach for treating *C. difficile* infection..."

"As expected, mice with the targeted ablation of HIF1α were significantly more susceptible to toxin-induced damage and inflammation," says Hirota. The mucosal specimens from patients with *C. difficile*-associated disease demonstrated an increase in the accumulation of HIF1α, as did the healthy biopsy specimens that were exposed to *C. difficile* toxins. The authors also showed that HIF1α accumulation in response to *C. difficile* toxins seems to be dependent on the presence of nitric oxide (NO). "We plan to assess exactly how HIF1α accumulation is occurring," says Hirota. "Our data suggest that NO derived from iNOS (inducible nitric oxide synthase) is involved in this process ... Furthermore, we want to determine the cellular mechanisms involved in *C. difficile*-toxin-induced upregulation of iNOS."

Hirota and colleagues also plan to "assess the role of intestinal epithelial HIF1 signaling in an infection model of *C. difficile*-associated disease". The authors suggest that patients who develop severe disease following *C. difficile* infection may have a reduced ability to induce HIF1 activation compared with patients who have minimal disease. Improving HIF1 activity could represent a novel approach for treating *C. difficile* infection.

Isobel Franks

Original article Hirota, S. A. *et al.* Hypoxia-inducible factor signaling provides protection in *Clostridium difficile*-induced intestinal injury. *Gastroenterology* **139**, 259–269 (2010)

© 2010 Macmillan Publishers Limited. All rights reserved