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MUCOSAL IMMUNOLOGY

Sick of the flu

Respiratory infection with influenza virus is often associated with gastroenteritis-like symptoms such as vomiting and diarrhoea. This study provides a mechanism for such symptoms by showing that CD4$^+$ T cells from the respiratory mucosa are recruited to the intestinal mucosa during influenza virus infection, where they induce dysbiosis that stimulates T helper 17 (T_H17) cell-mediated intestinal injury.

In mice infected intranasally with the A/Puerto Rico/8/34 (PR8) influenza virus strain, both the lung and small intestine, but not nonmucosal liver and kidney tissue, showed signs of severe injury. Influenza virus could not be detected in the small intestine of intranasally infected mice, and mice infected intragastrically with PR8 did not have injury to the small intestine; therefore, influenza virus does not directly cause injury to the intestinal mucosa.

> “influenza virus infection mediates intestinal injury by altering the composition of the intestinal microbiota”

S.Bradbrook/NPG

In support of an indirect effect of influenza virus on the intestines, Wang *et al.* showed that there was a decrease in the numbers of segmented filamentous bacteria, *Lactobacilli* and *Lactococci*, and an increase in the number of Enterobacteriaceae (including *Escherichia coli*), after intranasal PR8 infection. In mice treated with streptomycin (an antibiotic to which *E. coli* is sensitive), the intestines were protected from PR8-associated intestinal injury. Also, transferring the intestinal microbiota from PR8-infected mice to non-infected mice caused intestinal injury in the absence of influenza virus infection. Hence, respiratory influenza virus infection mediates intestinal injury by altering the composition of the intestinal microbiota, particularly the levels of *E. coli*.

So what causes intestinal dysbiosis in response to respiratory influenza virus infection? The authors showed that treating PR8-infected mice with a neutralizing antibody specific for CC-chemokine ligand 25 (CCL25), which is expressed by intestinal epithelial cells (IECs), prevented intestinal dysbiosis and reduced intestinal injury. Also, the number of CD4$^+$ T cells expressing the CCL25 receptor CCR9 was increased in the lamina propria of PR8-infected mice. These CCR9$^+$ cells were shown to be induced in the lungs in response to PR8-mediated expression of the enzyme ALDH1A2 (which regulates production of the CCR9-inducing factor retinoic acid) and they were then recruited to the intestines. The lung-derived CD4$^+$CCR9$^+$ effector T cells secrete interferon-γ in the intestines, which disrupts homeostasis of the microbiota.

As no intestinal injury was observed in PR8-infected mice deficient for interleukin-17A (IL-17A), the authors propose that T_H17 cells might be involved in the injurious effect of intestinal dysbiosis. Indeed, the number of T_H17 cells, as well as the expression of IL-17A and of the T_H17 cell-specific transcription factor RORγt, increased in the small intestine after intranasal PR8 infection. Treatment with streptomycin or an IL-17A-specific neutralizing antibody reduced IL-17A expression and intestinal injury, respectively, which shows that IL-17A production occurs downstream of intestinal dysbiosis. The final missing link between PR8-induced intestinal dysbiosis and T_H17 cell-mediated intestinal injury came from the demonstration that the altered intestinal microbiota of PR8-infected mice induced IL-15 expression by IECs, which in turn promoted T_H17 cell polarization in the small intestine.

These findings show that cross-talk between the respiratory and intestinal mucosae can occur through the specific recruitment of CD4$^+$ T cells. This interplay of immune cells between different mucosal sites lends support to the concept of a ‘common mucosal immune system’.

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ORIGINAL RESEARCH PAPER Wang, J. *et al.* Respiratory influenza virus infection induces intestinal immune injury via microbiota-mediated Th17 cell-dependent inflammation. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20140625 (2014)