VIRAL PATHOGENESIS

A brush with rotavirus

Infection with rotavirus is the leading cause of severe diarrhoeal disease and dehydration in infants worldwide, with almost 600,000 childhood deaths annually of which 82% are in developing countries. Despite decades of research, scientists are only now starting to piece together the pathogenic strategies used by this virus. Publishing in *Cellular Microbiology*, Beau *et al.* reveal that rotavirus infection of gastrointestinal enterocytes downregulates the biosynthesis of an important brush-border membrane (BBM)-associated hydrolase. This probably contributes directly to the malabsorption component of rotavirus diarrhoea.

Rotaviruses are non-enveloped icosahedral viruses with 11 double-stranded RNA gene segments protected by a triple-layered particle. This thick protein coat enables viruses to survive the onslaught of acid and digestive enzymes that are present in the gut. Rotaviruses specifically infect enterocytes — epithelial cells that are found at the tips of the villi in the ileum and have an apical BBM — that function to break up sugars and peptides and transport them into tissues during digestion. Diarrhoea during rotavirus infection results from various mechanisms, including malabsorption owing to enterocyte damage, activation of the enteric nervous system and the action of viral protein NSP4, which alters epithelial cell permeability and chloride secretion.

The latest research from the Servin laboratory aimed to pinpoint new cellular BBM functions that are affected by rotavirus infection. Using an enterocyte cell line they found that the activity of the dipeptidyl peptidase IV (DPP IV) hydrolase was dramatically reduced in rotavirus-infected cells. Monitoring labelled DPP IV by confocal microscopy revealed that mature DPP IV was correctly trafficked to the apical cell surface of the BBM in infected cells, albeit in reduced amounts. Moreover, since quantitative PCR revealed no change in DPP IV mRNA levels during viral infection, the reduction in enzyme activity was attributed by the authors to viral modulation of DPP IV mRNA translation. However, rotavirus does not effect a global shut-down of infected host-cell protein synthesis, as other key cellular proteins were produced in normal amounts. By specifically targeting the synthesis of DPP IV, the absorption of amino acids is drastically reduced, thereby contributing to diarrhoea.

Several important BBM proteins are targeted by rotavirus infection. Members of the same laboratory previously showed that rotavirus infection decreases expression of the sucrase-isomaltase (SI) enzyme complex in the BBM by altering its trafficking within the cell, and directly affects the function of the BBM-localized SGLT1 glucose symporter, both of which result in massive water loss into the intestinal lume n. Intriguingly, infection with pathogenic diffusely adherent *Escherichia coli* also blocks SI and DPP IV synthesis, so viral and bacterial diarrhoeal pathogens share this pathogenic tactic.

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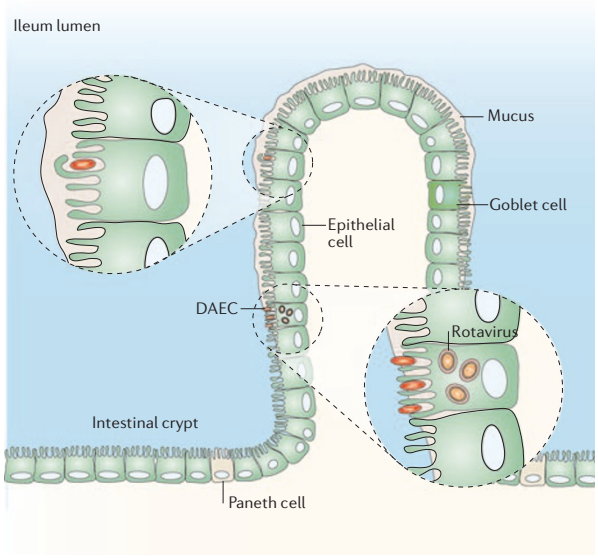

Villi are composed of absorptive epithelial cells (enterocytes). Interaction of extracellular DAEC with enterocytes blocks SI and DPP IV synthesis, whereas infection of these cells with rotavirus alters SI trafficking and downregulates DPP IV synthesis. DAEC, diffusely adherent *Escherichia coli*; SI, sucrase-isomaltase enzyme complex; DPP IV, dipeptidyl peptidase IV.

ORIGINAL RESEARCH PAPER Beau, I., Berger, A. & Servin, A. L. Rotavirus impairs the biosynthesis of brush-border-associated dipeptidyl peptidase IV in human enterocyte-like Caco-2/TC7 cells. *Cell. Microbiol.* 04 Oct 2006 (doi: 10.1111/j.1462–5822.2006.00827.x)
FURTHER READING Peiffer, I. *et al.* Impairments in enzyme activity and biosynthesis of brush border-associated hydrolases in human intestinal Caco-2/TC7 cells infected by members of the Afa/Dr family of diffusely-adhering *Escherichia coli* (DAEC Afa/Dr). *Cell. Microbiol.* **3**, 341–357 (2001) | Kaper, J. B., Nataro, J. P. & Mobley, H. L. T. Pathogenic *Escherichia coli*. *Nature Rev. Microbiol.* **2**, 123–140 (2004)