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COMMENTARY

Functional relationship between *Campylobacter concisus* and the stomach ecosystem in health and disease

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Our group has read with great interest the article by von Rosenvinge *et al.* (2013) on the characterization of the microbiota present in the stomach fluid using both 16S ribosomal DNA and ribosomal RNA sequencing. Gastric acidity and proteolytic enzymes act as a barrier to ingested microbes, thereby influencing the microbial ecology of the entire gastrointestinal tract (GIT). This is supported by the findings of von Rosenvinge *et al.* (2013) and others, who have shown that human gastric fluid harbors a microbiota with similar overall composition at the phylum level to that in other GIT locations. Thus, specific changes in the microbiota of the stomach could potentially be involved in gastric or intestinal manifestations such as Crohn's disease (CD) whose development is influenced by microbial dysbiosis (Man *et al.*, 2011).

In their study, von Rosenvinge *et al.* (2013) reported the transcriptional activity of members of Actinobacteria to be as low as 34%, while that of *Tannerella* to be as high as 680% in patients diagnosed with a range of clinical manifestations, including erythematous gastropathy, gastric ulcers and Barrett's esophagus. This was determined by calculating the ratio of relative 16S rRNA abundance over relative 16S rDNA abundance for each bacterial taxon identified. Actinobacteria are a large and ecologically diverse group of bacteria, some of which are pathogenic in humans. To understand their involvement in health and disease, functional studies on the roles of specific members of Actinobacteria with decreased transcriptional activity in the stomach (the oral habitants *Rothia dentocariosa* and *Actinomyces odontolyticus*) are required. Nevertheless, the data from von Rosenvinge *et al.* (2013) would suggest that the Actinomycineae (to which *Actinomyces* spp. belong) were transcriptionally most active in a patient (patient #44) with no endoscopic findings (RNA reads/DNA reads $=1.04$ vs 0.13 (patient #33), 0.27 (patient #52), 0.37 (patient #50) and 0.077 (patient #34)), and transcriptionally more active in patients not on proton pump inhibitors (1.04 and 0.37 vs 0.13, 0.27 and 0.077).

Tannerella forsythia has been previously detected in neonatal gastric aspirates (Gonzales-Marin *et al.*, 2011), and is considered a dental pathogen. The precise role of this bacterium in the stomach is less clear, and further work on this pathogen is required. Of particular interest was the finding that *Campylobacter* species, particularly *Campylobacter concisus* (Figure 1), were highly active (an increase of 444%) within the gastric fluid, irrespective of the pH (pH 1.0, 6.5 and 8.5; von Rosenvinge *et al.*, 2013). Previous studies have reported the isolation of *C. concisus* from human intestinal biopsies and fecal samples (Kaakoush and Mitchell, 2012), providing convincing evidence that *C. concisus* has the ability to survive stomach acid regardless of pH levels. The closely related pathogen *C. jejuni* induces an adaptive tolerance response when exposed to acid stress, and more importantly *C. jejuni* remains viable and maintains a helical shape following a 20-min exposure to pH 4.5 (Reid *et al.*, 2008). Thus, it is possible that some *C. concisus* strains utilize similar mechanisms of acid stress resistance, which enables them to thrive and remain metabolically active in the low pH levels of the gastric environment.

What role *C. concisus* may play in the stomach and why it is so highly active in this acidic environment is unclear; however, previous studies provide some insights into these questions. Using a *C. concisus*-specific PCR, we have previously shown a significantly higher prevalence of *C. concisus* DNA to be present in children with newly diagnosed CD (65%, 35/54) than in healthy controls (33%, 11/33, $P=0.008$) and non-CD controls (37%, 10/27, $P=0.03$) (Man *et al.*, 2010b). Interestingly, CD affects all sections of the GIT from the oral cavity to the anus, and a large percentage (89.5%) of the children with CD in our pediatric studies experienced L4 (upper GIT: esophagus and stomach) involvement (Man *et al.*, 2010b). The association of *C. concisus* with a form of CD that shows specific involvement of L4 raises the possibility that this pathogen may cause clinical pathology within the stomach.

C. concisus has also been detected in esophageal aspirate specimens and in distal esophageal mucosal samples from patients with Barrett's esophagus (Macfarlane *et al.*, 2007). Further, 3 of 25 patients in

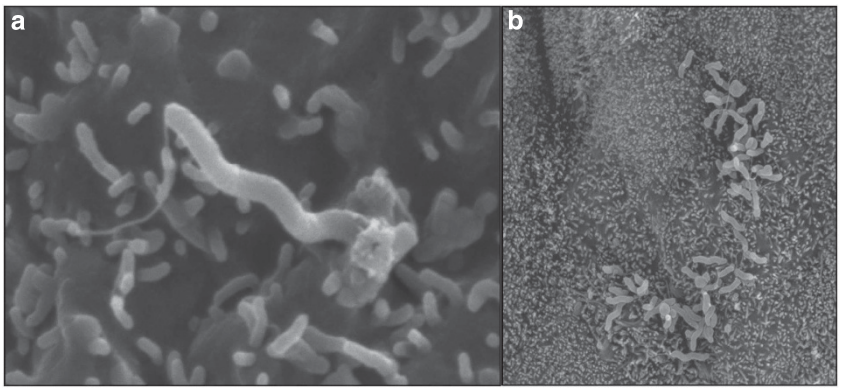

Figure 1 *C. concisus* is an emerging pathogen of the gastrointestinal tract. *C. concisus* invades a human intestinal epithelial cell, generating a membrane-ruffling phenomenon on the host cell membrane (**a**). *C. concisus* preferentially attaches to the intercellular junction of a human intestinal epithelium (**b**). Permission obtained from Oxford University Press © (Man *et al.*, 2010a).

the study by von Rosenvinge *et al.* (2013) were diagnosed with Barrett's esophagus. RNA-based amplicons were obtained for one of these patients (patient #50), and in this patient relative *Campylobacter* RNA reads were ~7.5 times more than *Campylobacter* DNA reads. The genetic diversity of *C. concisus* strains has been shown to contribute to the transcellular invasiveness of *C. concisus*, with strains isolated from chronic intestinal diseases being over 500 times more invasive than those isolated from acute intestinal diseases and healthy subjects (Kaakoush and Mitchell, 2012). While *in vitro* studies have shown that *C. concisus* strains adhere to and invade human intestinal epithelial cells (Kaakoush and Mitchell, 2012), further work is required to investigate whether *C. concisus* strains can invade epithelial cells of esophageal and gastric origin.

A further interesting finding within the study by von Rosenvinge *et al.* (2013) was the more pronounced activity of *C. concisus* in an immunocompromised patient as compared with the four samples from immunocompetent patients. *C. concisus* is highly immunogenic, and we have identified 31 *C. concisus* proteins to be immunoreactive in children with CD (Kaakoush and Mitchell, 2012). Moreover, patients with CD have elevated levels of *C. concisus*-specific immunoglobulin-G antibodies as compared with controls (Kaakoush and Mitchell, 2012), suggesting that the host immune system may be essential in controlling the levels of *C. concisus* in the GIT.

The functional relationship between *C. concisus* and other members of the stomach mucosa microbiota is unknown. The authors reported that the presence of *Helicobacter pylori* was not associated with significant differences in *C. concisus* levels (von Rosenvinge *et al.*, 2013). It is known that the response to *H. pylori* infection differs in individuals, and a subset of patients infected with *H. pylori* experience higher levels of acidity within the stomach while others remain asymptomatic or experience lower acidity (Suzuki and Moayyedi, 2013). Given the ability of *C. concisus* to remain active within a broad pH range (1.0–8.5) (von Rosenvinge *et al.*, 2013), this may explain the lack of effect observed by *H. pylori* on *C. concisus* levels.

The findings of von Rosenvinge *et al.* (2013), and the fact that *C. concisus* colonizes the oral cavity (Kaakoush and Mitchell, 2012), esophagus (Macfarlane *et al.*, 2007), the gastric mucosa (Bik *et al.*, 2006), as well as most areas of the intestines, including the ileum, jejunum, cecum and rectum (Kaakoush and Mitchell, 2012), indicate that this bacterium can colonize almost the entire GIT. Given this, elucidation of the role of commensal and pathogenic *C. concisus* strains within the GIT, the effect of these strains on the GIT microbiota, and the interplay between *C. concisus* strains with different pathogenic potential in the modulation of the host immune response would be of significant interest.

Conflict of Interest

The authors declare no conflict of interest.

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