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EDITORIAL

Oral *Campylobacter* species: Initiators of a subgroup of inflammatory bowel disease?

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Abstract

In recent years, a number of studies detected a significantly higher prevalence of *Campylobacter* species such as *Campylobacter concisus* (*C. concisus*) in intestinal biopsies and fecal samples collected from patients with inflammatory bowel disease (IBD) compared to controls. Most of these *Campylobacter* species are not of zoonotic origin but are human oral *Campylobacter* species. Bacterial species usually cause diseases in the location where they colonize. However, *C. concisus* and other oral *Campylobacter* species are associated with IBD occurring at the lower parts of the gastrointestinal tract, suggesting that these *Campylobacter* species may have unique virulence factors that are expressed in the lower parts of the gastrointestinal tract.

Key words: *Campylobacter concisus*; Oral *Campylobacter* species; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

Core tip: The human oral cavity is a reservoir of a number of *Campylobacter* species. Accumulated evidence suggests that some oral *Campylobacter* species such as *Campylobacter concisus* may be initiators of a subgroup of human inflammatory bowel disease.

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INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a group of chronic relapsing inflammatory diseases of the gastrointestinal tract. The most common clinical types of IBD are Crohn's disease (CD) and Ulcerative colitis (UC); the two forms of IBD differ in clinical presentation, distribution of inflammation in the gastrointestinal tract, endoscopic appearance and histology[1]. The cause of IBD is not well understood. It is thought

that the disease occurs in individuals with genetic predisposition when triggered by environmental factors[2]. The incidence of IBD is increasing worldwide[3]. Epidemiological studies suggest that environmental factors play a particularly important role in the increased incidence of IBD[4,5].

BACTERIAL FACTORS ASSOCIATED WITH IBD

Studies have shown that microbes in the gastrointestinal tract play a key role in the development of IBD. Colitis did not occur in animal models of IBD when raised germ-free, and the intestinal inflammation resolved in patients with CD after faecal stream diversion[6,7].

Extensive research has been conducted to search for the identities of the bacterial species that might contribute to the development of IBD. These include analyses of gut microbiome and investigations of associations between individual bacterial species and IBD. Studies of gut microbiome, which were performed by sequencing 16S rRNA genes, detected reduced bacterial species diversity and changed relative abundance (dysbiosis) in inflamed mucosal tissues of patients with IBD[8,9]. Recent studies suggest that such changes were due to the impact of host inflammatory responses on the resident microbes[10,11]. Indeed, bacterial species have different abilities in resisting the responses of the immune system and some may even use the by-products of inflammatory responses to boost their growth[10,12].

A number of individual bacterial species were found to be associated with patients with IBD, which were summarized in a recent review by Hold *et al*[13]. Whether the gut bacterial dysbiosis and individual bacterial species that are associated with IBD contribute to the pathogenesis of IBD are still under investigation.

DIFFERENTIAL ROLE OF BACTERIAL SPECIES IN THE PATHOGENESIS OF IBD

The generally accepted concept is that IBD is caused by multiple bacterial species. This concept may require some refinement in order to more clearly define the role of different bacterial species in the pathogenesis of IBD.

It may be more informative to divide bacterial species that are involved in the pathogenesis of IBD into two broad categories, initiators and exacerbators. The initiator bacterial species are those that instigate the inflammation in the early stage of IBD, while the exacerbator bacterial species are those that contribute to the on-going inflammation after the intestinal epithelial barrier is breached by a direct action of the initiators or by the inflammation initiated by the initiators. The dominant intestinal resident bacterial species, which have co-evolved with the host's mucosal immune system, most likely are exacerbators in the pathogenesis of IBD.

IBD is a group of diseases that have similar clinical manifestation and histopathology. Given this, the initiators of IBD may consist of several agents that have some common virulence factors. Individual cases may be initiated predominantly by one initiator bacterial species or by more than one initiator. The chronic and recurring nature of IBD suggests that IBD patients are frequently exposed to these initiators. CD can occur at any part of the gastrointestinal tract, suggesting that some initiators are present in the upper gastrointestinal tract. Accumulated evidence suggests that *Campylobacter concisus* (*C. concisus)* and a number of other oral *Campylobacter* species are possible initiators of a subgroup of human IBD.

MOST OF THE *CAMPYLOBACTER* SPECIES DETECTED IN PATIENTS WITH IBD ARE NOT OF ZOONOTIC ORIGIN BUT ARE HUMAN ORAL *CAMPYLOBACTER* SPECIES

To date, four studies have examined the intestinal prevalence of *Campylobacter* species in patients with CD and controls using *Campylobacter* genus PCR; three of which have detected a significantly higher intestinal prevalence of *Campylobacter* species in patients with CD as compared with the controls[14-17]. Three studies have examined the intestinal prevalence of *Campylobacter* species in patients with UC and controls using *Campylobacter* genus PCR, two of which detected a significantly higher intestinal prevalence of *Campylobacter* species in patients with UC compared with the controls[16-18].

At the single species level, three studies found a significantly higher intestinal prevalence of *C. concisus* in patients with CD as compared to controls[14-16]. Two studies found a significantly higher intestinal prevalence of *C. concisus* in patients with UC as compared to controls[16,18]. Furthermore, Mukhopadhya *et al*[18]. detected a significantly higher intestinal prevalence of *C. ureolyticus* in patients with UC as compared to controls.

In these studies, a total of eight *Campylobacter* species were detected, including *C. concisus*, *Campylobacter showae*, *Campylobacter hominis*, *Campylobacter gracilis*, *Campylobacter rectus*, *Campylobacter jejuni, Campylobacter curvus* and *Campylobacter ureolyticus*[14]. *C. concisus* was the most commonly detected species[14-18]. The majority of *Campylobacter* species detected in these studies were not of zoonotic origin but were previously reported human oral *Campylobacter* species (Table 1). These *Campylobacter* species do not have strong abilities in resisting the antimicrobial effects of bile, suggesting that the

Table 1 Most of *Campylobacter* species detected in the intestinal biopsies and fecal samples collected from patients with inflammatory bowel disease and controls are not of zoonotic origin but are human oral *Campylobacter* species

Campylobacter species	Human oral bacteria	2% ox-bile resistance	Urease activity	Motile
C. concisus	Yes	14%-50%	-	Yes
C. showae	Yes	-	-	Yes
C. hominis	No	60%-93%	-	No
C. gracilis	Yes	-	-	No
C. jejuni	No	60%-93%	-	Yes
C. ureolyticus	Yes	-	50%-100%	No
C. curvus	Yes	-	-	Yes
C. rectus	Yes	-	-	Yes

Information was obtained from[14-18,23,27,32,33]. *Campylobacter jejuni* (*C. jejuni*) refers to *C. jejuni* subsp. *jejuni*. *C. ureolyticus* has been isolated from various clinical sources including dental samples. - indicates 0%-11% positivity.

intestinal tract is not an optimal colonization site for these *Campylobacter* species in general (Table 1). *C. concisus* has a better ability in resisting bile compared to other oral *Campylobacter* species, about half of the *C. concisus* strains were able to grow in the presence of 2% ox bile (Table 1). Some *C. ureolyticus* strains are urease positive (Table 1). Of the six oral *Campylobacter* species detected in intestinal tissues, four species are motile (Table 1).

PATHOGENIC MECHANISMS OF *C. CONCISUS* AND OTHER ORAL *CAMPYLOBACTER* SPECIES

We hypothesized that some oral *C. concisus* strains may play a role in the development of IBD in 2010 and conducted continuous research to investigate this in the following years[19]. If *C. concisus* is involved in IBD, it is most likely an initiator. Indeed *C. concisus* does not appear to have strong abilities in resisting an inflammatory environment; there was a lower prevalence of this bacterium in areas with more severe inflammation compared to areas with less severe inflammation[14,20]. However, these *Campylobacter* species live in the human oral cavity, they may repeatedly colonize the lower parts of the intestinal tract.

Studies suggest that the enteric pathogenicity of *C. concisus* may be determined by both the characteristics of individual strains and an individual's intestinal environment. *C. concisus* normally colonizes the human oral cavity[19,21], some individuals are colonized with multiple oral *C. concisus* strains, which was more often seen in patients with active IBD[22]. *C. concisus* strains are very sensitive to low pH; most of the swallowed *C. concisus* bacteria are likely to have been killed by the acidic gastric juice. Bile is also a great inhibitor to the growth of *C. concisus*[23]. These observations in part explain the low isolation rate of *C. concisus* from fecal samples despite the bacterium being transported from the oral cavity to the lower parts of the gastrointestinal tract through swallowed saliva or food[24,25]. The inhibitory effect of bile to *C. concisus* growth is dose dependent[23]. This may be one of the reasons why *C. concisus* was more often detected in intestinal biopsies collected from descending colon and rectum of patients with IBD in a previous study by Mahendran *et al*[16]. A small number of oral *C. concisus* strains have greater abilities in resisting the antimicrobial effects of low pH and bile. The association between these strains and different phenotypic variants of IBD are under investigation.

In addition to gastric acid and bile, another environmental factor that may affect the colonization of *C. concisus* in the intestinal tract is H_2 gas. H_2 gas has a great impact on *C. concisus* growth. In laboratory cultivation, *C. concisus* does not grow under microaerobic conditions but has a very slow growth under anaerobic conditions[26,27]. The presence of H_2 gas enables *C. concisus* to grow under microaerobic conditions and markedly increases its growth under anaerobic conditions[26]. The atmospheric conditions in the human intestinal tract are microaerobic to anaerobic. Given this, *C. concisus* is likely to establish an intestinal colonization in individuals whose intestinal environment is able to provide a constantly available H_2 for *C. concisus* to use in their growth.

Normally, bacterial species cause disease in the location where they colonize. In contrast, *C. concisus* has an unusual disease association; it uses the human oral cavity as its natural colonization site, but is associated with IBD occurring at the lower parts of the gastrointestinal tract[14-16,18]. This unusual disease association pattern suggests that *C. concisus* may have unique virulence factors that are expressed in the intestinal environment. We previously identified a number of putative prophages in *C. concisus* genome[21], one of which is CON_phi2. CON_phi2 contains a gene that encodes zonula occludens toxin (Zot)[21]. Recently we detected the expression of Zot in *C. concisus* and found that *C. concisus* Zot has biological effects on Caco2 cells[28]. Whether enteric environmental factors affect the release of *C. concisus* Zot toxin and the pathogenic mechanisms of *C. concisus* Zot are current under investigation, which will shed lights on further understanding why *C. concisus*, an oral commensal bacterium, may contribute to inflammatory diseases in the lower parts of the gastrointestinal tract. The *zot* gene was also detected in *C. ureolyticus* strains isolated from amniotic fluid and vagina[29]. Whether *C. ureolyticus* strains isolated from the oral cavity of patients with IBD have the *zot* gene and the pathogenicity of *C. ureolyticus* Zot are currently under investigation, which may reveal a common pathogenic mechanism shared by a number of *Campylobacter* species.

KOCH'S POSTULATES AND THE ROLE OF *C. CONCISUS* IN IBD

A question that we have often encountered in examining the role of *C. concisus* in IBD was whether the relationship between this bacterium and IBD has fulfilled Koch's postulates. In 1880s, Robert Koch proposed some criteria, which were called Koch's postulates, to determine the causative relationship between a microbe and a disease. Despite its contribution to the development of microbiology, these postulates have limitations, which have been discussed by other researchers[30]. IBD is not a single disease and *C. concisus* is not a typical pathogen. *C. concisus* is a bacterium that is present in everyone's oral cavity and some strains have acquired additional virulence factors such as toxins encoded by prophages. The pathogenicity of this bacterium is determined not only by the virulence of individual strains but also an individual's gastrointestinal environmental factors. Given this, Koch's postulates are not suitable to assess the relationship between *C. concisus* and IBD.

IMPORTANCE OF IDENTIFYING BACTERIAL SPECIES THAT INITIATE IBD AND SUGGESTIONS TO CONSIDER *C. CONCISUS* AND OTHER ORAL *CAMPYLOBACTER* SPECIES AS A TARGET IN MANAGEMENT OF HUMAN IBD

Due to the unknown identities of bacterial species that initiate the disease, the treatment of IBD is predominantly symptomatic management, involving anti-inflammation and suppression of patient's immune system. As a result, relapse in IBD is frequent and in some cases, surgery is required. As IBD is a group of diseases, it is important to identify initiators that are responsible for individual cases, which will enable the development of treatment strategies that are suitable for individual patients to reduce relapse and surgery.

Some strategies targeting *C. concisus* and other oral *Campylobacter* species may be incorporated into IBD management. One suggestion is to reduce the load of *C. concisus* and other *Campylobacter* species in the oral cavity using topical treatments. Oral cavity is the natural colonization site of *C. concisus* and a number of other *Campylobacter* species detected in the intestinal tissues of patients with IBD. Reduction of the load of *C. concisus* and other *Campylobacter* species in the oral cavity reduces the possibility of these bacteria colonizing the lower parts of the gastrointestinal tract. The main advantage of this strategy is that it is non-invasive and unlikely to disturb the balance of intestinal microbiota.

The second suggestion is to eradicate *C. concisus* and other oral *Campylobacter* species using antibiotics in patients with IBD, particularly in patients with frequent relapses and multiple surgeries. We previously found that *C. concisus* was not detected in saliva samples collected from IBD children who received metronidazole or ciprofloxacin one month prior[31]. However, *C. concisus* was detected in most of saliva samples (6/7, 86%) collected from IBD children who had antibiotics treatment two months prior[31]. These data showed that the two antibiotics that were used in treatment of some cases of IBD, metronidazole and ciprofloxacin, only had inhibited the growth of oral *C. concisus* or eradicated it from the oral cavity temporarily. An effective antibiotic therapy that can be used to eradicate *C. concisus* needs to be developed. Prior to using a given antibiotic to treat patients with IBD, whether the antibiotic induces *C. concisus* and other oral *Campylobacter* species to produce prophage toxins should also be examined.

FUTURE STUDIES

Accumulated evidence suggests that translocation of *C. concisus* and other *Campylobacter* species from their natural colonization site, the oral cavity, to the lower parts of the gastrointestinal tract may initiate mucosal inflammation there. Further studies investigating the unique pathogenic mechanisms of *C. concisus* and other oral *Campylobacter* species are needed, which will shed light on the understanding of how oral *Campylobacter* species may initiate the development of chronic mucosal inflammatory conditions such as IBD. Diagnostic methods that can accurately identify IBD cases which are caused by translocation of *C. concisus* or other oral *Campylobacter* species should be developed. In addition, effective therapies in reducing or eradicating oral *Campylobacter* species should be established. These strategies will provide useful information in assisting the clinical management of individual IBD cases.

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