Abstract
Investigation of the possible role of Campylobacter concisus (C. concisus) in inflammatory bowel disease (IBD) is an emerging research area. Despite the association found between C. concisus and IBD, it has been difficult to explain how C. concisus, a bacterium that is commonly present in the human oral cavity, may contribute to the development of enteric diseases. The evidence presented in this review shows that some C. concisus strains in the oral cavity acquired zonula occludens toxin (zot) gene from a virus (prophage) and that C. concisus Zot shares conserved motifs with both Vibrio cholerae Zot receptor binding domain and human zonulin receptor binding domain. Both Vibrio cholerae Zot and human zonulin are known to increase intestinal permeability by affecting the tight junctions. Increased intestinal permeability is a feature of IBD. Based on these data, we propose that a primary barrier function defect caused by C. concisus Zot is a mechanism by which zot-positive C. concisus strains may trigger the onset and relapse of IBD.

Key words: Campylobacter concisus; Inflammatory bowel disease; Zonula occludens toxin; Tight junctions; Intestinal permeability

Core tip: Campylobacter concisus (C. concisus) is an oral bacterium that was previously shown to be associated with inflammatory bowel disease (IBD). Evidence presented in this review shows that some strains of C. concisus acquired zonula occludens toxin (zot) gene from a virus (prophage), suggesting that a primary barrier function defect caused by C. concisus Zot is a mechanism by which zot-positive C. concisus strains may trigger the onset and relapse of IBD.

INTRODUCTION
Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract[5]. The two major clinical forms of IBD are Crohn’s disease (CD) and ulcerative colitis (UC). The etiology of IBD is not fully understood. Multiple contributors including genetic
in 97% (57/59) of saliva samples collected from healthy individuals aged 3-60 years old by polymerase chain reaction (PCR) targeting 16S rRNA gene and cultured from 75% (44/59) of these saliva samples using a filtration method. A study from Petersen et al[8] also detected a high prevalence of C. concisus in the human oral cavity: in this study C. concisus was detected in 100% of saliva samples (11/11) collected from healthy individuals by a PCR targeting 16S rRNA gene. Despite its high prevalence in the human oral cavity, C. concisus is not a dominant oral bacterial species[1].

In comparison to the high isolation of C. concisus from saliva samples, the isolation rates of C. concisus from fecal samples collected from healthy individuals were much lower. Using the filtration method, Engberg et al[10] isolated C. concisus from 2.8% (3/107) of fecal samples and Nielsen et al[9] did not isolate C. concisus from any of 108 fecal samples collected from healthy individuals. The low isolation rates of C. concisus from fecal samples suggest that the human intestinal tract of healthy individuals is a less optimal site for C. concisus colonization compared to the oral cavity.

To date, C. concisus has not been detected in any healthy animals. In a study examining the presence of Campylobacter species in fecal samples collected from 70 healthy pet dogs using a quantitative PCR targeting the 60 kDa chaperonin gene, Chaban et al[11] detected seven different campylobacter species but not C. concisus. Various campylobacter species have been detected in fecal samples collected from animals or birds, but C. concisus was not detected[3,10,11]. Lynch et al[12] isolated C. concisus from 10% (18/185) of chicken meat and 3% of beef meat (6/186) samples. However, whether chicken and cattle are natural hosts of C. concisus cannot be determined from these data.

C. concisus has been detected in some animals with gastrointestinal disorders. Petersen et al[8] detected C. concisus in 12.5% (1/8) of saliva samples from pet cats with dental diseases by PCR targeting the 16S rRNA gene[8]. In addition, Chaban et al[11] detected C. concisus in fecal samples of 9% of dogs with diarrhea (6/65).

The collective data suggest that humans are the natural host of C. concisus, with the human oral cavity being the primary colonization site (Table 1).
COLONIZATION OF ORAL C. CONCISUS STRAINS

C. concisus strains colonizing the human oral cavity are greatly diverse. On examination of oral C. concisus strains isolated from individual patients with IBD and healthy controls, it was found that C. concisus strains isolated from each individual had unique protein patterns on sodium dodecyl sulphate polyacrylamide gel electrophoresis. Furthermore, some individuals were colonized with multiple C. concisus strains in the oral cavity, with as many as three different C. concisus strains having been isolated from individual patients with IBD or healthy controls. A significantly higher number of patients with active IBD were colonized with multiple C. concisus strains in the oral cavity compared to healthy controls.

PREVALENCE OF C. CONCISUS IN THE INTESTINAL TRACT OF PATIENTS WITH IBD AND HEALTHY CONTROLS

A number of studies have examined the prevalence of C. concisus in the intestinal tract of patients with IBD using PCR methods. Most of these studies detected a significantly higher prevalence of C. concisus DNA in patients with IBD and controls. The reported detection rates of C. concisus by PCR in enteric samples (biopsies and fecal samples) were 33%-69% in patients with IBD and 2%-38% in controls. Analysis of the data in these studies revealed a number of interesting findings.

Firstly, different PCR strategies affect the detection of C. concisus in enteric samples. This was best seen in the study conducted by Man et al., who compared the prevalence of C. concisus in fecal samples collected from 54 children with CD, 33 healthy controls and 27 non-IBD controls using two different PCR methods. The first PCR method employed campylobacter genus specific PCR (primers C412F/C1288R) and sequencing the PCR products to determine campylobacter species. The second PCR method was a nested PCR, using campylobacter genus specific PCR (primers C412F/C1288R) followed by C. concisus specific PCR (primers Concisus F/Concisus R). These two PCR methods yielded very different results in detection of C. concisus in the same samples. The prevalence of C. concisus in children with CD, healthy controls and non-IBD controls detected by C. concisus genus specific PCR...
was 19% (10/54), 12% (4/33) and zero (0/27) respectively. The nested PCR greatly increased the detection of *C. concisus* in the same cohort of samples, with the prevalence of *C. concisus* being 65% (35/54) in children with CD, 33% (11/33) in healthy controls and 37% (10/27) in non-IBD controls. The nested PCR, but not the genus specific PCR, detected a significantly higher prevalence of *C. concisus* in children with CD as compared to healthy controls[39] (Table 3). Indeed, in studies revealing a significant difference in intestinal prevalence of *C. concisus* between patients with IBD and controls, nested PCR was used to examine all of the samples or part of the samples[17-21].

Secondly, collection of multiple intestinal biopsies increases the detection of intestinal prevalence of *C. concisus*. A study by Mahendran et al[44] showed that in comparison to the collection of one biopsy, the collection of four biopsies from each individual greatly increased the detection of *C. concisus* (Figure 2).

Thirdly, despite the increased prevalence of *C. concisus* detected by PCR in the intestinal tract of patients with IBD, the isolation rates of *C. concisus* from intestinal biopsies of patients with IBD were low (3%-7.7%)[17,20,21]. This suggests that *C. concisus* detected in most of the enteric samples were at a low number or in a nonculturable state.

### ADVERSE EFFECTS OF *C. CONCISUS* ON INTESTINAL EPITHELIAL CELLS

A number of adverse effects of *C. concisus* on intestinal epithelial cells have been described. Using *in vitro* cell culture models (Caco2 cells or HT-29 cells), epithelial adhesion and invasion, damage of the barrier function and up-regulation of Toll-like receptors-4 expression by *C. concisus* have been reported. Different strains showed varying degrees of ability to induce such adverse effects[13,22-28]. The underlying molecular mechanisms responsible for these effects have not yet been investigated.

### C. CONCISUS ZOT GENE AND IBD

Mahendran et al[44] examined the prevalence of *zot* gene in 56 oral *C. concisus* strains isolated from saliva of 19 patients with IBD and 20 healthy controls. This study showed that 30% (17/56) of the oral *C. concisus* strains carried the *zot* gene. The *zot*-positive *C. concisus* strain was present in 55% (6/11) of patients with active IBD and 40% (8/20) of healthy controls. Some IBD patients with active disease 18% (2/11) were colonized with multiple *zot*-positive *C. concisus* strains in the oral cavity. Interestingly, polymorphic forms of the *C. concisus zot* gene resulting in the substitution of valine at amino acid position 270 were found to be associated with active IBD.

The *zot* gene was first discovered in *Vibrio cholerae* where it is carried by a filamentous prophage[26,27]. The *zot* gene in *V. cholerae* is required for phage production; a *V. cholerae* strain with *zot* gene mutation did not produce phage particles into the culture supernatant[28]. The *V. cholerae Zot* toxin was shown to increase intestinal permeability and to be associated with mild to moderate diarrhea[26,29,30].

Previous studies have found a human intestinal Zot analogue, namely zonulin, which is a physiological regulator that increases the intestinal permeability[31,32].

### C. CONCISUS ZOT GENE IS A COMPONENT OF A CHROMOSOMALLY INTEGRATED PUTATIVE PROPHAGE

Stothard et al[33] established a visual database of bacterial...
chromosome maps in which *C. concisus* strain 13826 (Accession No. CP000792.1) was included. Stothard et al. [33] identified a region from nucleotide position 1576683 to 1615449 (38767 bp) in the genome of *C. concisus* strain 13826 as an “incomplete prophage”. In this region, 39 genes with open reading frames were identified, with four of these genes encoding integrases and 10 genes encoding phage-like proteins [33].

The genetic structures of this “incomplete prophage” region are shown in Figure 3A and the proteins encoded by genes in this region are shown in Table 4. We compared the genes within this region using publicly available softwares [34,35]. A number of genes that have identical nucleotide sequences, including CCC13826_1099, CCC13826_0190, CCC13826_0191, CCC13826_0185, CCC13826_2082 and CCC13826_2077 were annotated with identical protein names.

Interestingly, the region that was considered as an “incomplete prophage” by Stothard et al. [33] turned out to be four putative prophages, each beginning with a phage integrase (Figure 3 and Table 4). The first prophage had a genome size of 5.2 kb, which contained seven protein-encoding genes. The second prophage and third prophage were identical, each having a genome size of 9.6 kb consisting of 10 protein-encoding genes. The fourth prophage contained 11 protein-encoding genes with a genome size of 8.6 kb. We named the first prophage CON_phi1, the second prophage and third prophage CON_phi2 and CON_phi3. The zot gene is a component of CON_phi2. Comparison of the proteins encoded by genes in CON_phi2 with that encoded by genes in CTX phage, the phage that carries the zot gene in *V. cholera*, did not show high similarities except for the Zot protein (data not shown), suggesting the CON_phi2 is a previously uncharacterised prophage.

A study by Kaakoush et al. [36] found that two hypothetical proteins encoded by CCC13826_0191 and CCC13826_0188 in *C. concisus* strain 13826 and *V. cholerae* strain 86015 have 47% and 46% similarity respectively to *C. concisus* Zot. Here we found that CCC13826_0191 is a gene of CON_phi3 and CCC13826_0188 is a gene of an additional putative prophage, which was named CON_phi4. A number of genes in CON_phi3 and CON_phi4 had high similarities, however, CON_phi4 did not contain the gene that corresponding to CCC13826_0188 in CON_phi3 (Table 5).

### IDENTIFICATION OF CONSERVED MOTIFS SHARED BY *C. CONCISUS* ZOT AND ZONULIN/ZOT RECEPTOR BINDING DOMAINS

Kaakoush et al. [36] compared Zot sequences in *C. concisus* strain 13826 and *V. cholerae* strain 86015 and reported that
the biological active domain (FCIGRL) previously found in V. cholerae Zot was not found in C. concisus Zot. In this review, we compared the sequence of C. concisus Zot with human zonulin receptor binding domain and V. cholerae Zot receptor binding domain previously reported[32,37]. Interestingly, we found that C. concisus Zot shares conserved motifs with both the human zonulin receptor binding domain and the V. cholerae Zot receptor binding domain (Table 6). These data suggest that C. concisus Zot may increase intestinal permeability using a mechanism that is similar to the human zonulin and V. cholerae Zot, affecting the tight junctions through proteinase activated receptor 2 activation[47,48]. The motif “GRFLSYHG” is located at amino acid position 123-130 in C. concisus Zot, which was found in all oral zot-positive C. concisus strains that we previously isolated as well as in the C. concisus strain 13826[16]. The polymorphisms of C. concisus zot gene that Mahendran et al.[16] previously detected were not in the receptor binding domain, suggesting that these polymorphisms may impact on the function of C. concisus Zot, if there is any, using a different mechanism rather than affecting the binding of C. concisus Zot to the receptor.

### INCREASED INTESTINAL PERMEABILITY IN PATIENTS WITH IBD

Increased intestinal permeability is a feature of both CD and UC[19-43]. While epithelial cell death and proinflammatory cytokines may damage the intestinal epithelial barrier during active disease, evidence shows that increased intestinal permeability may precede the initial onset or relapse of IBD. An early study from Hollander et al.[39] reported that increased intestinal permeability was detected not only in patients with CD but also in their healthy relatives. A family history of IBD is a known risk factor for IBD[40,41]. Irvine et al.[41] reported that an individual with a family history of CD had elevated intestinal permeability eight years prior to the onset of clinical symptoms and diagnosis of CD. Wyatt et al.[41] measured the intestinal...
permeability in patients with quiescent CD and found that those with increased intestinal permeability were at a significantly higher risk of clinical relapse. These data suggest that increased intestinal permeability occurred prior to the onset and relapse of the disease may be a possible aetiological factor of IBD.

**C. CONCISUS ZOT: A POTENTIAL TRIGGER OF IBD THROUGH CAUSING PRIMARY BARRIER DEFECT**

The human zonulin and V. cholerae Zot toxin are known to increase intestinal permeability through affecting the tight junctions[11,12,20]. In this review, we found that C. concisus Zot has conserved motifs shared by the zonulin/Zot binding receptor domains. Given this, it is very likely that C. concisus Zot also affects the tight junctions.

Based on the information obtained from previous publications and the analysis that we have performed in this review, we propose a mechanism by which C. concisus, an oral bacterium, may trigger the onset or relapse of IBD: that some oral C. concisus strains acquire zot gene from a virus (prophage). With the human oral cavity as the reservoir of C. concisus, repeated intestinal colonization of C. concisus and release of C. concisus Zot due to prophage induction may occur, which is likely to result in a prolonged primary epithelial barrier defect and translocation of macromolecules such as luminal microbes and their products. In genetically susceptible individuals, this may trigger the development of IBD.

Damage to the intestinal epithelial tight junctions may also lead to the development of diarrhea. Indeed, in addition to its association with IBD, C. concisus has been frequently isolated from non-IBD-related diarrheal stool samples[13,14,46].

If some oral C. concisus strains are indeed involved in the development of human IBD, the question as to why the lesions of IBD occur more often in the intestinal tract rather than in the oral cavity. For example, the expression of C. concisus Zot may require induction of prophage from the C. concisus genome. As prophage induction usually occurs when bacterial cells are under stressful conditions[45], the fact that C. concisus uses the human oral cavity as its primary colonization site suggests that the oral cavity is not a stressful site for C. concisus. However, as the C. concisus travels to the more hostile lower parts of the gastrointestinal tract, the stressful environment may trigger the induction of C. concisus prophage.

Another possible factor that may reduce the pathogenic effect of C. concisus Zot in the oral cavity is that the epithelium in the oral cavity is a stratified squamous epithelium, either keratinized or non-keratinized[49]. In contrast, the intestinal epithelium is a simple columnar epithelium[48]. The impact on permeability caused by Zot, even it is expressed in the oral cavity, in multiple layers of squamous epithelium may not be as evident as that in the single layered columnar epithelium.

**C. CONCISUS ZOT: A POTENTIAL ENVIRONMENTAL FACTOR CONTRIBUTING TO THE INCREASED RISK OF IBD IN INDIVIDUALS WITH A FAMILY HISTORY OF IBD**

A family history of IBD is a risk factor for developing IBD[49]. In addition to genetic factors, environmental factors have been shown to be involved in the increased incidence of IBD in members with a family history of this disease[49,50]. We suggest that C. concisus Zot is one such factor. This suggestion is based on the findings that the higher numbers of the relatives of patients with IBD have increased intestinal permeability and that some oral C. concisus strains carry the zot gene that encodes a toxin known to promote this[11,12,20]. This hypothesis remains to be further assessed by examining the correlation between colonization of zot-positive C. concisus strains and the increased intestinal permeability in family members of patients with IBD.
CONCLUSION

The evidence presented in this review shows that some C. concisus strains colonizing the human oral cavity acquired zot gene from a virus (prophage). We are currently examining the biologic activities of C. concisus Zot, the expression of Zot in zot-positive C. concisus strains isolated from patients with IBD and controls as well as the presence of C. concisus Zot in the oral cavity and intestinal tract of patients with IBD and controls, which will provide further information in understanding the role of C. concisus Zot in IBD and other human diseases.

ACKNOWLEDGMENTS

The authors would like to thank Vikneswari Mahendran and Jenny Norman for providing the scanning electron microscopic picture of C. concisus.

REFERENCES

1. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. Nature 2011; 474: 307-317 [PMID: 21677747 DOI: 10.1038/nature10299]
2. Bernstein CN, Wajda A, Svensson LW, MacKenzie A, Koebohoj M, Jackson M, Fedorak R, Israel D, Blanchard JF. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006; 101: 1559-1568 [PMID: 16863561 DOI: 10.1111/j.1572-0241-2006.00630.x]
3. Vandamme P, Dewhurst FE, Paster BJ, On SLW. Genus I. Campylobacter. In: Garrity GM, Brenner DJ, Krieg NR, Stal P, editors. Bergey’s Manual of Syst Bacteriol. 2 ed. New York: Springer, 2005: 1147-1160
4. Tanner ACR, Badger S, Lai CH, Listgarten MA, Visconti RA, Socransky SS. Wolinella gen-nov, Wolinella-succinogenes (Vibrio-succinogenes-wolin et-al) comb-nov, and description of Bacteroides-gracilis sp-nov, Wolinella-recta sp-nov, Campylobacter-concisus sp-nov, and Eikenella-corrodens from humans with periodontal disease. Int J Syst Bacteriol 1981; 31: 432-445 [DOI: 10.1128/ij.sbm.1981.31.2.432]
5. Zhang L, Budiman V, Day AS, Mitchell H, Lemberg DA, Riordan SM, Grimm MC, Leach ST, Ismail Y. Isolation and detection of Campylobacter concisus from saliva of healthy individuals and patients with inflammatory bowel disease. J Clin Microbiol 2010; 48: 2965-2967 [PMID: 20519479 DOI: 10.1128/jcm.02991-09]
6. Petersen RF, Harrington CS, Kortegaard HE, On SL. A PCR-DGGE method for detection and identification of Campylobacter, Helicobacter, Arcobacter and related Epsilonbacteria and its application to saliva samples from humans and domestic pets. J Appl Microbiol 2007; 103: 2601-2615 [PMID: 17916160 DOI: 10.1111/j.1365-2672.2007.03515.x]
7. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhurst FE. Defining the normal bacterial flora of the oral cavity. J Clin Microbiol 2005; 43: 5721-5732 [PMID: 16272510 DOI: 10.1128/JCM.43.11.5721-5732.2005]
8. Engberg J, On SL, Harrington CS, Gerner-Smidt P. Prevalence of Campylobacter, Arcobacter, Helicobacter, and Sutterella spp. in human fecal samples as estimated by a reevaluation of isolation methods for Campylobacters. J Clin Microbiol 2000; 38: 286-291 [PMID: 10618103]
9. Nielsen HL, Ejlersen T, Engberg J, Nielsen H. High incidence of Campylobacter concisus in gastroenteritis in North Jutland, Denmark: a population-based study. Clin Microbiol Infect 2013; 19: 445-450 [PMID: 22512739 DOI: 10.1111/j.1469-0691.2012.03852.x]
10. Chaban B, Ngeleka M, Hill JE. Detection and quantification of 14 Campylobacter species in pet dogs reveals an increase in species richness in feces of diarrheic animals. BMC Microbiol 2010; 10: 73 [PMID: 20219122 DOI: 10.1186/1471-2180-10-73]
11. Moore JE, Corcoran D, Dooley JS, Fanning S, Lucey B, Matsuda M, McDowell DA, Megraud F, Millar BC, O’Mahony R, O’Riordan L, O’Rourke M, Rao JR, Rooney PJ, Sails A, Whyte P, Campylobacter. Vet Res 2005; 36: 351-382 [PMID: 15845230]
12. Lynch OA, Cagney C, McDowell DA, Duffy G. Occurrence of fastidious Campylobacter spp. in fresh meat and poultry using an adapted cultural protocol. Int J Food Microbiol 2011, 150: 171-177 [PMID: 21855156 DOI: 10.1016/j.ijfoodmicro.2011.07.037]
13. Ismail Y, Mahendran V, Octavia S, Day AS, Riordan SM, Grimm MC, Lan R, Lemberg D, Tran TA, Zhang L. Investigation of the enteric pathogenic potential of oral Campylobacter concisus strains isolated from patients with inflammatory bowel disease. PLoS One 2012; 7: e38217 [PMID: 22664940]
14. Mahendran V, Tan YS, Riordan SM, Grimm MC, Day AS, Lemberg DA, Octavia S, Lan R, Zhang L. The Prevalence and Polymorphisms of Zonula Occludens Toxin Gene in Multiple Campylobacter concisus Strains Isolated from Saliva of Patients with Inflammatory Bowel Disease and Controls. PLoS One 2013; 8: e75525 [PMID: 24086553 DOI: 10.1371/journal.pone.0075525]
15. Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. J Prostheth Dent 2001; 85: 162-169 [PMID: 11208206 DOI: 10.1067/mpr.2001.113778]
16. Haag LM, Fischer A, Otto B, Pickert K, Kühl AA, Göbel UB, Bereswill S, Heimesaat MM. Intestinal microbiota shifts towards elevated commensal Escherichia coli loads abrogate colonization resistance against Campylobacter jejuni in mice. PLoS One 2012; 7: e39988 [PMID: 22563475]
17. Zhang L, Man SM, Day AS, Leach ST, Lemberg DA, Dutt S, Stormon M, Otley A, O’Loughlin EV, Magoffin A, Ng PH, Mitchell H. Detection and isolation of Campylobacter species other than C. jejuni from children with Crohn’s disease. J Clin Microbiol 2009; 47: 453-455 [PMID: 19052183 DOI: 10.1128/JCM.01949-08]
18. Man SM, Zhang L, Day AS, Leach ST, Lemberg DA, Mitchell H. Campylobacter concisus and other Campylobacter species in children with newly diagnosed Crohn’s disease. Inflamm Bowel Dis 2010; 16: 1008-1016 [PMID: 19885905 DOI: 10.1002/ibd.21157]
19. Mukhopadhyya I, Thomson JM, Hansen R, Berry SH, El-Omar EM, Hold GL. Detection of Campylobacter concisus and other Campylobacter species in colonic biopsies from adults with ulcereative colitis. PLoS One 2011; 6: e21490 [PMID: 21738679]
20. Mahendran V, Riordan SM, Grimm MC, Tran TA, Major J, Kaakoush NO, Mitchell H, Zhang L. Prevalence of Campylobacter species in adult Crohn’s disease and the preferential colonization sites of Campylobacter species in the human intestine. PLoS One 2011; 6: e25417 [PMID: 21966525 DOI: 10.1371/journal.pone.0025417]
21. Hansen R, Berry SH, Mukhopadhyya I, Thomson JM, Saunders KA, Nicholl CE, Bisset WM, Loganathan S, Mahdi G, Kastner-Cole D, Barclay AR, Bishop J, Flynn DM, McGrogan P, Russell RK, El-Omar EM, Hold GL. The microaerophilic microbiota of de-novo paediatric inflammatory bowel disease: the BISCUT study. PLoS One 2013; 8: e58825 [PMID: 23554935]
22. Kalischuk LD, Inglis GD. Comparative genotypic and pathogenic examination of Campylobacter concisus isolates from diarrheic and non-diarrheic humans. BMC Microbiol 2011; 11: 53 [PMID: 21406111]
Is small intestinal permeability, and its expression in coeliac disease. Fasano A, Torklin PA, McWilliam H, Valentin F, Wallace IM, Wilm A, Larkin MA. 21546353 DOI: 10.1093/molbev/msr121

parsimony methods. S. MEGA5: molecular evolutionary genetics analysis using picture atlas of annotated bacterial genomes. B, Cruz J, Ellison M, Wishart DS. BacMap: an interactive Stothard P. 2000; 113 Pt 24: 4435-4440 [PMID: 11082037]

fected Immun (zot) encoding a new toxin produced by Vibrio cholerae. Fasano A, Ketley J, Kaper JB. Cloning of a gene 10588910 DOI: 10.1006/mpat.1999.0312

cellular localization. 10.1073/pnas.88.12.5242

function by apoptosis induction in HT-29/B6 intestinal epithelial cells. Proc PLoS One 2011; 6: e23588 [PMID: 21887334 DOI: 10.1371/journal.pone.0023858]

T dumpster 2 expression of TLR4, MD-2, TLR2, TLR5 and COX-2 in effects of oral and enteric Campylobacter concisus strains on expression of TLR4, MD-2, TLR2, TLR5 and COX-2 in HT-29 cells. Proc PLoS One 2013; 8: e56888 [PMID: 23437263 DOI: 10.1371/journal.pone.0056888]

Baudry B, Fasano A, Ketley J, Kaper JB. Cloning of a gene (zot) encoding a new toxin produced by Vibrio cholerae. Infection Immun 1992; 60: 428-434 [PMID: 1730472]

Levine MM, Kaper JB, Herrington D, Losonsky G, Morris JG, Clements ML, Black RE, Tall B, Hall R. Volunteer studies of deletion mutants of Vibrio-cholerae O1 prepared by recombinant techniques. Infect Immun 1988; 56(1): 161-167

Fasano A, Not T, Wang W, Uzzau S, Berti I, Tommasini A, Baudry B, Pumplin DW, Wasserman SS, Tall BD, Kruiningen HJ, Nuttens MC, Cortot A. Inflammatory bowel disease: an emerging Campylobacter spp.: the tip of the iceberg. Clin Microbiol Newsl 2006; 28: 49-56 [DOI: 10.1016/j.clinmicnews.2006.03.004]

Lastovic AJ. Emerging Campylobacter spp.: the tip of the iceberg. Clin Microbiol Newsl 2006; 28: 49-56 [DOI: 10.1016/j.clinmicnews.2006.03.004]

Imamovic L. Campylobacter upsaliensis, C. sputorum sputorum and C. concisus as common causes of diarrhoea in Swedish children. Scand J Infect Dis 2007; 40(1): 161-167 [PMID: 1742-4658:2010.07987.x]

Goldblum SE, Rai U, Tripathi A, Thakar M, De Leo L, Di Toro N, Not T, Ramachandran R, Puche AC, Hollenberg MD, Fasano A. The active Zot domain (aa 288-293) increases ZO-1 and myosin 9C serine/threonine phosphorylation, alters interaction between ZO-1 and its binding partners, and induces tight junction disassembly through proteinase activated receptor 2 activation. FASEB J 2011; 25: 144-158 [PMID: 20852064 DOI: 10.1096/fj.10-158972]

Tripathi A, Lammers KM, Goldblum S, Shea-Donohue T, Netzir-Arnett S, Buzza MS, Antalis TM, Vogel SN, Zhao A, Yang S, Arrietta MC, Meddings JB, Fasano A. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2. Proc Natl Acad Sci USA 2009; 106: 16779-16804 [PMID: 19805376 DOI: 10.1073/pnas.090673106]

Hollander D, Vadheim CM, Bretholz E, Petersen GM, Delahunty T, Rotter JI. Increased intestinal permeability in patients with Crohn’s disease and their relatives. A possible etiologic factor. Ann Intern Med 1986; 105: 883-885 [PMID: 3777715 DOI: 10.1072/s0003-4819-105-6-883]

Lamins KM, Goldblum S, Shea-Donohue T, Netzir-Arnett S, Buzza MS, Antalis TM, Vogel SN, Zhao A, Yang S, Arrietta MC, Meddings JB, Fasano A. Identification of human zonulin, a physiological modulator of tight junctions, as prehaptoglobin-2. Proc Natl Acad Sci USA 2009; 106: 16779-16804 [PMID: 19805376 DOI: 10.1073/pnas.090673106]

Irwine EJ, Marshall JK. Increased intestinal permeability precedes the onset of Crohn’s disease in a subject with familial risk. Gastroenterology 2000; 119: 1740-1744 [PMID: 11113005 DOI: 10.1053/gast.2000.22231]

Welcker K, Martin A, Kölle P, Siebeck M, Gross M. Increased intestinal permeability in patients with inflammatory bowel disease. Eur J Med Res 2004; 9: 456-460 [PMID: 15568111]

Wyatt J, Vogelsang H, Hübl W, Waldhöfer T, Lochs H. Intestinal permeability and the prediction of relapse in Crohn’s disease. Lancet 1993; 341: 1437-1439 [PMID: 8099141 DOI: 10.1016/0140-6736(93)90882-H]

Halme I, Paavola-Säkkî P, Turunen U, Lappalainen M, Farkkila M, Kontula K, Family and twin studies in inflammatory bowel disease. World J Gastroenterol 2006; 12: 3668-3672 [PMID: 16773682]

Lindblom GB, Sjögren E, Hansson-Westerberg J, Kaierer B. Campylobacter upsaliensis, C. sputorum sputorum and C. concisus as common causes of diarrhoea in Swedish children. Scand J Infect Dis 1995; 27: 187-188 [PMID: 7660089 DOI: 10.1053/gast.2000.22231]

Lastovic AJ. Emerging Campylobacter spp.: the tip of the iceberg. Clin Microbiol Newsl 2006; 28: 49-56 [DOI: 10.1016/j.clinmicnews.2006.03.004]

Imamovic L, Muniesa M. Characterizing RecA-independent induction of Shiga toxin2-encoding phages by EDTA treatment. PLoS One 2012; 7: e32393 [PMID: 22393404 DOI: 10.1371/journal.pone.0032939]

Eroschenko VP. Di Fiore’s atlas of histology with functional correlations, 9 ed. Canada: Susan Katz, 2003

Bennett RA, Rubin PH, Present DH. Frequency of inflammatory bowel disease in offspring of couples both presenting with inflammatory bowel disease. Gastroenterology 1991; 100: 1638-1643 [PMID: 2019369]

Comes MC, Gower-Rousseau C, Colombel JF, Belaïche J, Van Kuizingen HJ, Nuttens MC, Cortot A. Inflammatory bowel disease in married couples: 10 cases in Nord Pas de Calais region of France and Liège county of Belgium. Gut 1994; 35: 1516-1518 [PMID: 7959244 DOI: 10.1136/gut.35.9.1316]

P-Reviewers: Actis GC, Azuma YT, Capasso R
S-Editor: Gou SX L-Editor: A E-Editor: Wang CH
