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FACTORS AND REGULATION OF CAMPYLOBACTER VIRULENCE

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ABSTRACT

Campylobacter jejuni and related species are important human pathogens, causing acute human enter colitis, and they are the most common cause of food-borne diarrhoea in many industrialized countries. Previous infection with certain strains of C. jejuni is also linked with the development of the neurological disorder Guillain - Barre syndrome (GBS). Relatively little is understood of the mechanisms of C. jejuni-associated disease despite its importance as a human pathogen,. The recent release of the complete genome sequence of C. jejuni strain NCTC 11168, together with new strategies for directed and random mutagenesis. It has allowed a better insight into some of the genetic determinants of C. jejuni virulence. In this review paper current knowledge on factor and regulation of C. jejuni infection is summarized.

Keyword: Campylobacter, C. jejuni, Virulence, Factors, Regulation.

1. INTRODUCTION

The primarily source of C. jejuni/coli infections in human is believed to be the handling and/or consumption of contaminated meat, especially poultry meat. However, contact with pets and livestock, the consumption of contaminated water or raw milk and travelling in high prevalence areas are also considered risks factors in human disease. The human pathogens Campylobacter jejuni and Campylobacter coli are causative agents of acute human enter colitis. They are the most common cause of food-borne diarrhoea in many developed countries.

Understanding of Campylobacter mechanisms associated disease is still relatively poor despite its importance as a human pathogen. The major target of agencies responsible for food safety world-wide is control of Campylobacter in the food chain nowadays.

2. CAMPYLOBACTER VIRULENCE FACTORS:

Fig 1 shows the colonization phase when several putative virulence factors are predicted to be expressed by enteric campylobacter while colonizing the intestines.

2.1 Motility and Chemotaxis

Colonization of the intestine requires the ability to move into the mucus layer covering the intestinal cells. Campylobacter motility is conferred by the polar flagella, and combined with their `cork-screw' form allows them to efficiently penetrate this mucus barrier. The flagellum of C. jejuni consists of an unsheathed polymer of flagellin subunits, which are encoded by the adjacent *fla*A and *fla*B genes which are subject to both antigenic variation and phase variation and show a very high degree of sequence identity (95%). The flaA gene is expressed at much higher levels (from a σ^{28} promoter) than the flaB gene (from a σ^{54} promoter), and the C. jejuni flagellum consists normally of FlaA protein. However, a C. jejuni $flaA^{+}$ and $flaB^{+}$ mutant showed slightly decreased motility, demonstrating a role of FlaB in flagellar function. The flagella of C. jejuni were tested successfully as part of a subunit vaccine in mice, indicating the importance of flagella in the pathogenesis of C. jejuni [1, 33, 53, 59, 61, 62, and 81].

Several accessory proteins are involved in export, assemblyvand expression of flagella. Campylobacter jejuni contains several genes encoding proteins homologous to E. coli proteins involved in flagellar expression. However, experimental evidence to prove their role in flagellar biosynthesis or motility is still lacking. Several aflagellated mutants have been used to demonstrate the importance of flagella to C. jejuni colonization and pathogenesis [58, 99].

Chemotaxis is the ability to detect and move up or down chemical gradients. Both motility and chemotaxis are essential for C. jejuni colonization, as non-chemotactic mutants were unable to colonize the intestine in animal models. Campylobacter jejuni is attracted to mucins, L-serine and L-fucose, whereas bile acids are repellants. The regulatory gene cheY was identified as the affected gene in a motile, non-invasive mutant of C. jejuni, and is thought to be involved in general modulation of C. jejuni virulence genes. A C. jejuni cheY mutant was more adherent and invasive than the wild-type strain, but unable to colonize ferrets or cause disease [38, 83, 109].

2.2 Adhesion and Invasion

An important feature in C. jejuni pathogenesis is its binding and entry in host cells. Upon infection, C. jejuni crosses the mucus layer covering the epithelial cells and adheres to these cells, and a subpopulation subsequently invades the epithelial cells. The invasion of epithelial cells can lead to the mucosal damage and inflammation often seen in Campylobacter infection; it is not clear whether inflammation has a direct role in epithelial damage and/or diarrhoea. In vitro and in vivo experiments have demonstrated that C. jejuni is capable of invading epithelial cells, although the invasive ability of strains differs. Fresh clinical isolates tend to invade at higher frequencies, and continued in vitro passaging reduces the invasiveness of strains, which are also capable of translocation across cell layers but transcytosis maybe a direct consequence of host cell invasion [20, 44, 45].

The first C. jejuni determinants identified to be involved in adherence and invasion were the flagella. Adhesion and invasion are dependent on both motility and flagellar expression, as C. jejuni mutants showing reduced motility due to paralysed flagella showed reduced adherence, and absence of invasion. This indicated that, while flagella are involved in adherence, other adhesins must be involved in subsequent internalization. Invasion is also thought to be involved in triggering inflammation, as invasion of C. jejuni was required for induction of several markers of inflammation such as the important proinflammatory cytokine interleukin 8. Adhesion by bacterial pathogens is often mediated by fimbrial structures. The pilus-like appendage has been shown to be an artifact of the presence of bile salts in growth medium. Other adhesins identified are the PEB1 and CadF proteins [16, 19, 29, 37, 100, 108].

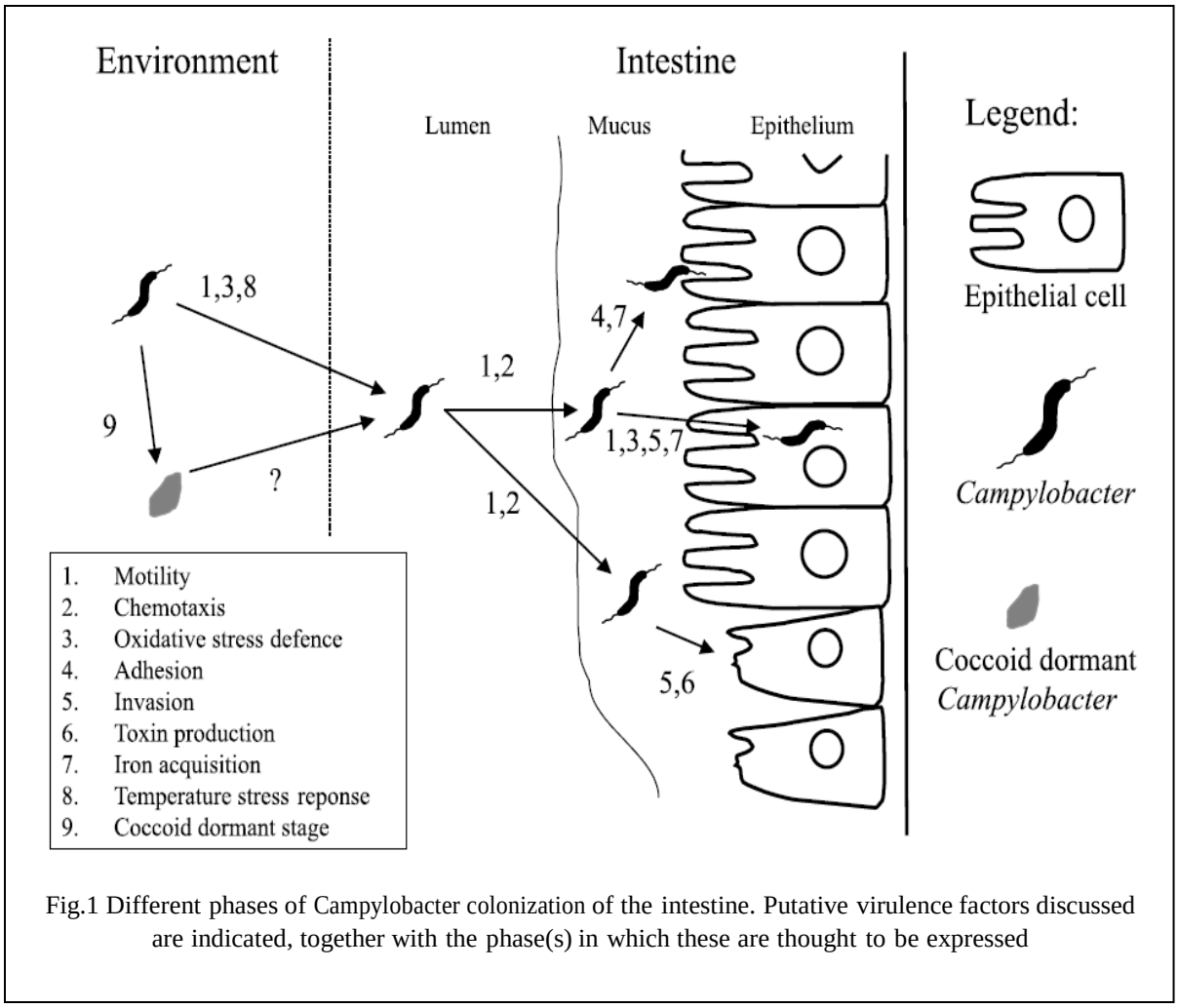

Fig.1 Different phases of Campylobacter colonization of the intestine. Putative virulence factors discussed are indicated, together with the phase(s) in which these are thought to be expressed

Invasion of C. jejuni has been tested in vitro using several cell lines of intestinal origin, such as INT-407, HEp-2 and differentiated Caco-2 cells. Differentiated Caco-2 cells form tight junctions and produce apical surface enzymes. Campylobacter jejuni invasion is both dependent on de novo synthesized C. jejuni proteins as well as host cell signal transduction. Co-cultivation of C. jejuni and INT-407 cells lead to the production and secretion of at least eight proteins including the CiaB protein [20, 45, 47].

Processes in the host cell are also heavily involved in internalization of C. jejuni. So far all (random) mutagenesis techniques have only allowed the identification of motilityrelated genes as genetic determinants involved in C. jejuni invasion (flaA, flaB, pflA, cheY) [65, 104].

2.3 Toxins

Strain and assay differences are responsible for the differences in the range of reported toxic activities. Cytolethal distending toxin activity causes certain cell types (such as HeLa cells and Caco-2 cells) to become slowly distended, which progresses into cell death. While most C. jejuni strains have a relatively high CDT activity, C. coli strains show mostly low activity. CDT cytotoxicity is caused by a G2 phase cell cycle block in the host cell through blocking of the CDC2 kinase involved in entry into mitosis. CDT involvement in diarrhoea was proposed to disturb the survival or maturation of crypt cells into functional villus epithelial cells and cause a temporary erosion of the villus and a subsequent loss of absorptive functions. A C. jejuni cdtB mutant was unaffected in enteric colonization abilities in adult severe combined immunodeficient mice, but demonstrated impaired invasiveness into blood, spleen and liver tissues [70, 71, 98].

2.4 Iron Acquisition

The ability to acquire the essential nutrient iron from the host contributes to bacterial pathogenesis. The concentration of free iron in host tissues is too low to support bacterial growth, as iron is complexed into haem compounds and to transferrin (in serum) and lactoferrin (at mucosal surfaces); this iron limitation constitutes a non-specific host defence. Campylobacter jejuni can utilize a relatively low number of iron compounds. It does not produce siderophores, but is able to use the siderophores ferrichrome and enterochelin produced by other organisms. It is also able to use haem compounds, which might be released at the site of inflammation [23, 69].

Gram-negative ferric iron acquisition systems usually consist of an outer membrane (OM) receptor, which transports the iron compound over the OM, a periplasmic binding protein and an inner membrane (IM) ABC transporter consisting of a permease and ATP-binding protein, while ferrous iron transport is usually accomplished by a single IM protein. Campylobacter jejuni expresses several ferric iron acquisition systems upon growth in iron-restricted conditions. So far, a haemin/haemoglobin uptake system (chuABCD) (Rock et al. 1999) and an enterochelin transport system lacking an OM receptor (ceuBCDE) (Richardson and Park 1995) have been identified and demonstrated to be involved in iron acquisition; both are present in all strains tested to date. The C. jejuni genome also encodes one putative ferrous iron transport system, a homologue of the E. coli FeoB protein. Escherichia coli and H. pylori feoB mutants were unable to colonize the intestine and stomach respectively in a mouse model.This indicates that while the FeoB protein might not be essential under in vitro conditions, it could have an important role in colonization by campylobacters [8, 26, 34, 74].

2.5 Surface polysaccharide structures

The outer membrane constituents lipo-oligosaccharide (LOS) and lipopolysaccharide (LPS) form a major compo- nent of the Gram-negative outer membrane, and are important virulence factors involved in serum

resistance, endotoxicity and adhesion. Lipooligosaccharide is composed of two regions, a lipid A molecule joined to a core oligosaccharide, and LPS additionally contains an O-chain consisting of repeating oligosaccharide. Campylobacter jejuni strains always express LOS, but on Western blots probed with strain-specific antibodies it was also shown that some strains had an O-chain-like ladder [25, 101].

The C. jejuni surface polysaccharide structures and flagella have been shown to be sialylated, which is thought to be responsible for the ganglioside mimicry leading to Guillain-BarreÂ syndrome (GBS) which is a serious autoimmune disorder of the peripheral nervous system, and is one of the most common causes of acute flaccid paralysis. A C. jejuni strain of serotype O:19, associated with GBS, had two genes encoding sialyltransferases, whereas strain NCTC 11168 (serotype O:2) had only one copy, which showed much lower sialyltransfer- ase activity. There have also probably been internal genetic rearrangements and heterologous DNA uptake, leading to the strain differences. To assess the role of these gene clusters, further analysis of the composition of these loci in strains of different serotypes will be required as an analysis of gene content variation has revealed differences between strains [28, 58, 63].

2.6 Oxidative stress defence

Campylobacters are microaerophilic bacteria, which means that they have to deal with toxic oxygen metabolites produced during normal metabolism, during transmission or when in contact with the host immune defences. Campylobacter jejuni and C. coli share the same oxidative stress defence systems, which can be divided into superoxide stress defence and peroxide stress defence. The main component of the C. jejuni superoxide stress defence is the superoxide dismutase (SOD) protein SodB encoded by the sodB gene.). The peroxide stress defence consists mainly of two proteins, the catalase (KatA) and alkyl hydroperoxide reductase (AhpC, also named Tsa or TsaA) proteins. Neither the C. jejuni ahpC mutant or the C. jejuni and C. coli katA mutants were affected under standard in vitro growth conditions. An accessory component of the peroxide stress defence may be one of the two ferredoxin proteins of C. jejuni (FdxA). A C. jejuni fdxA mutant showed decreased aerobic survival similar to that of the C. jejuni ahpC mutant, but was not affected in specific oxidative stress defence. A model has been proposed in which the FdxA protein is used to reduce the oxidized AhpC protein, thus recycling it. Further investigation is necessary to determine any direct role of peroxide stress defence in colonization and pathogenesis [68, 73, 80, 92].

2.7 Heat shock response

Campylobacter jejuni and C. coli must be able to respond to a change in temperature, as they can be found in the avian gut, where the normal temperature is 42°C, as well as temperatures in human hosts (37°C) and during transmission in water, milk or on meat (4°C or varying temperatures). The thermal stress response of bacteria is mostly carried out by the induction of the expression of heat shock proteins (HSPs). These HSPs have an important function in thermotolerance as well as in the response to other stresses by acting as chaperones to promote the folding of most cellular proteins and proteolysis of potentially deleterious, misfolded proteins. Several HSPs have been identified in C. jejuni, including the GroESL, DnaJ, DnaK and ClpB proteins. The

importance of the C. jejuni thermal stress response is also indicated by the link between thermoregulation and chicken colonization through the RacR regulatory protein [6, 46, 86].

3. CAMPYLOBACTER VIRULENCE REGULATION

3.1 Iron Responsive Regulation

Iron is an essential nutrient for all living organisms, but is also capable of generating toxic oxygen metabolites. Therefore iron homoeostasis is of vital importance to the cell. In host tissues the free iron concentration is mostly too low to allow bacterial growth. This iron restriction, a non-specific host defence mechanism, is used by several bacterial pathogens as a signal for the coordinated expression of virulence factors through the Fur protein. Genes regulated in response to iron usually include toxins, haemolysins and iron acquisition genes, but can also include (virulence) genes not related to iron metabolism. The C. jejuni Fur protein is the major iron-responsive regulator, as a C. jejuni fur mutant was not able to regulate the expression of all known iron acquisition systems, and also grew significantly slower under standard in vitro growth conditions. However, there was still iron-responsive gene regulation in a C. jejuni fur mutant, indicating the presence of a second iron-responsive regulator. This second iron-responsive regulator was shown to be the PerR protein, which regulates the expression of the peroxide stress defence proteins AhpC and KatA. A C. jejuni perR mutant was hyper-resistant to peroxide stress inducers [18, 91, 95].

3.2 Two- component and other regulatory systems

Two-component regulatory systems are widely spread in bacteria, and have an important role in signal transduction of environmental stimuli. They usually consist of a histidine protein kinase (HPK) sensor that is located in the IM with a cytoplasmic kinase domain site, and a response regulator (RR) that is phosphorylated by the HPK. The phosphory- lated RR interacts with the promoters of its target genes and regulates their expression coordinately. A C. jejuni racR mutant showed a decreased growth rate at 42°C but not at 37°C compared with the wild-type strain. With a PCR-based approach several putative RR genes were isolated from C. jejuni [107].

4. CONCLUSION

During the past 30 years Campylobacter spp. has become the focus of several research groups around the world. Improved diagnostic methods have demonstrated its import- ance in human disease, and it has been recognized as a major public health burden in industrialized countries. Despite the attention it has received, many questions remain to be answered. A systematic search for C. jejuni factors involved in colonization and invasion should allow the identification of factors important for pathogenesis of C. jejuni infection. Several other Campylobacter species, especially the recently recognized human pathogen Campylobacter upsaliensis, require further research and application of the techniques developed for C. jejuni.

5. REFERENCES

1. Alm, R.A., Guerry, P. and Trust, T.J. (1993) The Campylobacter sigma 54 flaB flagellin promoter is subject to environmental regulation. Journal of Bacteriology 175, 448-4455.
2. Baillon, M.L.A., van Vliet, A.H.M., Ketley, J.M., Constantinidou, C. and Penn, C.W. (1999), An iron-regulated alkyl hydroperoxide reductase (AhpC) confers aerotolerance and oxidative stress resistance to the microaerophilic pathogen Campylobacter jejuni. Journal of Bacteriology 181, 4798-4804.
3. Beier, D. and Frank, R. (2000) Molecular characterization of twocomponent systems of Helicobacter pylori. Journal of Bacteriology 182, 2068-2076.
4. Bersudsky, M., Rosenberg, P., Rudensky, B. and Wirguin, I. (2000) Lipopolysaccharides of a Campylobacter coli isolate from a patient with Guillain-Barre syndrome display ganglioside mimicry. Neuromuscular Disorders 10, 182-186.
5. Black, R.E., Levine, M.M., Clements, M.L., Hughes, T.P. and Blaser, M.J. (1988) Experimental Campylobacter jejuni infection in humans. Journal of Infectious Diseases 157, 472-479.
6. Bras, A.M., Chatterjee, S., Wren, B.W., Newell, D.G. and Ketley, J.M. (1999a) A novel Campylobacter jejuni two-component regulatory system important for temperature-dependent growth and colonization. Journal of Bacteriology 81, 3298-3302.
7. Bras, A.M. and Ketley, J.M. (1999b) Transcellular translocation of Campylobacter jejuni across human polarised epithelial monolayers. FEMS Microbiology Letters 179, 209-215.
8. Braun, V., Hantke, K. and Koster, W. (1998) Bacterial iron transport: mechanisms, genetics, and regulation. Metal Ions in Biological Systems 35, 67-145.
9. Bukau, B. (1993) Regulation of the Escherichia coli heat shock response. Molecular Microbiology 9, 671-680.
10. Caldwell, M.B., Guerry, P., Lee, E.C., Burans, J.P. and Walker, R.I. (1985) Reversible expression of ¯agella in Campylobacter jejuni. Infection and Immunity 50, 941-943.
11. Cappelier, J.M., Minet, J., Magras, C., Colwell, R.R. and Federighi, M. (1999) Recovery in embryonated eggs of viable but nonculturable Campylobacter jejuni cells and maintenance of ability to adhere to HeLa cells after resuscitation. Applied and Environmental Microbiology 65, 5154-5157.
12. Chan, V.L., Louie, H. and Bingham, H.L. (1995) Cloning and transcription regulation of the ferric uptake regulatory gene of Campylobacter jejuni TGH9011. Gene 164, 25-31.
13. Chang, N. and Taylor, D.E. (1990) Use of pulsed-field agarose gel electrophoresis to size genomes of Campylobacter species and to construct a SalI map of Campylobacter jejuni UA580. Journal of Bacteriology 172, 5211-5217.
14. Central Public Health Laboratory (1999) Common gastrointestinal infections, England and Wales. Communicable Diseases Report Weekly 9, 11-13.
15. Doig, P., Kinsella, N., Guerry, P. and Trust, T.J. (1996a) Characterization of a posttranslational modification of Campylobacter flagellin - identification of a sero-specific glycosyl moiety. Molecular Microbiology 19, 379-387.
16. Doig, P., Yao, R.J., Burr, D.H., Guerry, P. and Trust, T.J. (1996b) An environmentally regulated pilus-like appendage involved in Campylobacter pathogenesis. Molecular Microbiology 20, 885-894.

17. Endtz, H.P., Ang, C.W., van Den Braak, N., Duim, B., Rigter, A., Price, L.J., Woodward, D.L., Rodgers, F.G., Johnson, W.M., Wagenaar, J.A., Jacobs, B.C., Verbrugh, H.A. and van Belkum, A. (2000) Molecular characterization of Campylobacter jejuni from patients with Guillain-Barre and Miller Fisher Syndromes. Journal of Clinical Microbiology 38, 2297-2301.

18. Escolar, L., Perez-Martin, J. and de Lorenzo, V. (1999) Opening the iron-box: transcriptional metalloregulation by the Fur protein. Journal of Bacteriology 181, 6223-6229.

19. Everest, P.H., Cole, A.T., Hawkey, C.J., Knutton, S., Goossens, H., Butzler, J.P., Ketley, J.M. and Williams, P.H. (1993) Roles of leukotriene B4, prostaglandin E2, and cyclic AMP in Campylobacter jejuni-induced intestinal ¯uid secretion. Infection and Immunity 61, 4885-4887.

20. Everest, P.H., Goossens, H., Butzler, J.P., Lloyd, D., Knutton, S., Ketley, J.M. and Williams, P.H. (1992) Differentiated Caco-2 cells as a model for enteric invasion by Campylobacter jejuni and C. Coli. Journal of Medical Microbiology 37, 319-325.

21. Eyigor, A., Dawson, K.A., Langlois, B.E. and Pickett, C.L. (1999a) Detection of cytolethal distending toxin activity and cdt genes in Campylobacter spp. isolated from chicken carcasses. Applied and Environmental Microbiology 65, 1501-1505.

22. Eyigor, A., Dawson, K.A., Langlois, B.E. and Pickett, C.L. (1999b) Cytolethal distending toxin genes in Campylobacter jejuni and Campylobacter coli isolates: detection and analysis by PCR. Journal of Clinical Microbiology 37, 1646-1650.

23. Field, L.H., Headley, V.L., Payne, S.M. and Berry, L.J. (1986) Influence of iron on growth, morphology, outer membrane protein composition, and synthesis of siderophores in Campylobacter jejuni. Infection and Immunity 54, 126-132.

24. Fry, B.N., Feng, S., Chen, Y.Y., Newell, D.G., Coloe, P.J. and Korolik, V. (2000) The galE gene of Campylobacter jejuni is involved in lipopolysaccharide synthesis and virulence. Infection and Immunity 68, 2594-2601.

25. Fry, B.N., Korolik, V., ten Brinke, J.A., Pennings, M.T.T., Zalm, R., Teunis, B.J.J., Coloe, P.J. and van der Zeijst, B.A.M. (1998) The lipopolysaccharide biosynthesis locus of Campylobacter jejuni 81116. Microbiology 144, 2049-2061.

26. Galindo, M.A., Day, W.A., Raphael, B.H. and Joens, L.A. (2001) Cloning and characterisation of a Campylobacter jejuni iron uptake optron. Current Microbiology 42, 139-143.

27. Gaynor, E.C., Ghori, N. and Falkow, S. (2001) Bile induced `pili' in Campylobacter jejuni are bacteria-independent antifacts of the culture medium. Molecular Microbiology 39, 1546-1549.

28. Gilbert, M., Brisson, J.R., Karwaski, M.F., Michniewicz, J., Cunningham, A.M., Wu, Y., Young, N.M. and Wakarchuk, W.W. (2000) Biosynthesis of ganglioside mimics in Campylobacter jejuni OH4384. Journal of Biological Chemistry 275, 3896-3906.

29. Grant, C.C., Konkel, M.E., Cieplak, W. Jr and Tompkins, L.S. (1993) Role of flagella in adherence, internalization, and translocation of Campylobacter jejuni in nonpolarized and polarized epithelial cell cultures. Infection and Immunity 61, 1764-1771.

30. Grant, K.A., Belandia, I.U., Dekker. N., Richardson, P.T. and Park, S.F. (1997) Molecular characterization of pldA, the structural gene for a phospholipase A from Campylobacter coli, and its contribution to cell-associated hemolysis. Infection and Immunity 65, 1172-1180.

31. Grant, K.A. and Park, S.F. (1995) Molecular characterization of katA from Campylobacter jejuni and generation of a catalase-deficient mutant of Campylobacter coli by interspecific allelic exchange. Microbiology 141, 1369-1376.

32. Guerry, P., Doig, P., Alm, R.A., Burr, D.H., Kinsella, N. and Trust, T.J. (1996) Identification and characterization of genes required for post-translational modification of Campylobacter coli VC167 flagellin. Molecular Microbiology 19, 369-378.

33. Guerry, P., Logan, S.M., Thornton, S. and Trust, T.J. (1990) Genomic organization and expression of Campylobacter flagellin genes. Journal of Bacteriology 172, 1853-1860.

34. Guerry, P., Perez-Casal, J., Yao, R., McVeigh, A. and Trust, T.J. (1997) A genetic locus involved in iron utilization unique to some Campylobacter strains. Journal of Bacteriology 179, 3997-4002.

35. Harris, L.A., Logan, S.M., Guerry, P. and Trust, T.J. (1987) Antigenic variation of Campylobacter flagella. Journal of Bacteriology 169, 5066-5071.

36. Hazeleger, W.C., Wouters, J.A., Rombouts, F.M. and Abee, T. (1998) Physiological activity of Campylobacter jejuni far below the minimal growth temperature. Applied and Environmental Microbiology 64, 3917-3922.

37. Hickey, T.E., Baqar, S., Bourgeois, A.L., Ewing, C.P. and Guerry, P. (1999) Campylobacter jejuni-stimulated secretion of interleukin-8 by INT407 cells. Infection and Immunity 67, 88-93.

38. Hugdahl, M.B., Beery, J.T. and Doyle, M.P. (1988) Chemotactic behavior of Campylobacter jejuni. Infection and Immunity 56, 1560-1566.

39. Jones, D.M., Sutcliffe, E.M. and Curry, A. (1991) Recovery of viable but non-culturable Campylobacter jejuni. Journal of General Microbiology 137, 2477-2482.

40. Karlyshev, A.V., Linton, D., Gregson, N.A., Lastovica, A.J. and Wren, B.W. (2000) Genetic and biochemical evidence of a Campylobacter jejuni capsular polysaccharide that accounts for penner serotype specificity. Molecular Microbiology 35, 529-541.

41. Ketley, J.M. (1997) Pathogenesis of enteric infection by Campylobacter. Microbiology 143, 5-21.

42. Kinsella, N., Guerry, P., Cooney, J. and Trust, T.J. (1997) The flgE gene of Campylobacter coli is under the control of the alternative sigma factor sigma (54). Journal of Bacteriology 179, 4647-4653.

43. Konkel, M.E., Garvis, S.G., Tipton, S.L., Anderson, D.E. and Cieplak, W. (1997) Identification and molecular cloning of a gene encoding a fibronectin-binding protein (CadF) from Campylobacter jejuni. Molecular Microbiology 24, 953-963.

44. Konkel, M.E., Hayes, S.F., Joens, L.A. and Cieplak, W. Jr (1992a) Characteristics of the internalization and intracellular survival of Campylobacter jejuni in human epithelial cell cultures. Microbial Pathogenesis 13, 357-370.

45. Konkel, M.E. and Joens, L.A. (1989) Adhesion to and invasion of HEp-2 cells by Campylobacter spp. Infection and Immunity 57, 2984-2990.

46. Konkel, M.E., Kim, B.J., Klena, J.D., Young, C.R. and Ziprin, R. (1998) Characterization of the thermal stress response of Campylobacter jejuni. Infection and Immunity 66, 3666-3672.

47. Konkel, M.E., Kim, B.J., Rivera-Amill, V. and Garvis, S.G. (1999) Bacterial secreted proteins are required for the internalization of Campylobacter jejuni into cultured mammalian cells. Molecular Microbiology 32, 691-701.

48. Konkel, M.E., Mead, D.J., Hayes, S.F. and Cieplak, W. (1992b) Translocation of Campylobacter jejuni across human polarized epithelial cell monolayer cultures. Journal of Infectious Diseases 166, 308-315.
49. Korolik, V., Fry, B.N., Alderton, M.R., van der Zeijst, B.A.M. and Coloe, P.J. (1997) Expression of Campylobacter hyoilei lipo-oligosac- charide (LOS) antigens in Escherichia coli. Microbiology 143, 3481-3489.
50. Kuroki, S., Haruta, T., Yoshioka, M., Kobayashi, Y., Nukina, M. and Nakanishi, H. (1991) Guillain-BarreÂ syndrome associated with Campylobacter infection. Pediatric Infectious Diseases Journal 10, 149-151.
51. Kuroki, S., Saida, T., Nukina, M., Haruta, T., Yoshioka, M., Kobayashi, Y. and Nakanishi, H. (1993) Campylobacter jejuni strains from patients with Guillain-BarreÂ syndrome belong mostly to Penner serogroup 19 and contain beta-N-acetylglucosamine residues. Annals of Neurology 33, 243-247.
52. Lee, L.H., Burg, E. III, Baqar, S., Bourgeois, A.L., Burr, D.H., Ewing, C.P., Trust, T.J. and Guerry, P. (1999) Evaluation of a truncated recombinant flagellin subunit vaccine against Campylo- bacter jejuni. Infection and Immunity 67, 5799-5805.
53. Lee, A., O'Rourke, J.L., Barrington, P.J. and Trust, T.J. (1986) Mucus colonization as a determinant of pathogenicity in intestinal infection by Campylobacter jejuni: a mouse cecal model. Infection and Immunity 51, 536-546.
54. Linton, D., Karlyshev, A.V., Hitchen, P.G., Morris, H.R., Dell, A., Gregson, N.A. and Wren, B.W. (2000) Multiple N-acetyl neuraminic acid synthetase (neuB) genes in Campylobacter jejuni: identification and characterization of the gene involved in sialylation of lipo-oligosaccharide. Molecular Microbiology 35, 1120-1134.
55. Matz, C.M., van Vliet, A.H.M., Ketley, J.M. and Penn, C.W. (1999) Characterisation of expression of flagellar gene flhB in Campylobacter jejuni. In Abstracts 10th International Workshop on CHRO, Baltimore, MD. University of Maryland. p. 84 (Abstract Cp8).
56. Medema, G.J., Schets, F.M., van de Giessen, A.W. and Havelaar, A.H. (1992) Lack of colonization of 1 day old chicks by viable, non- culturable Campylobacter jejuni. Journal of Applied Bacteriology 72, 512-516.
57. Miller, S., Pesci, E.C. and Pickett, C.L. (1993) A Campylobacter jejuni homolog of the LcrD/FlbF family of proteins is necessary for flagellar biogenesis. Infection and Immunity 61, 2930-2936. Nachamkin, I., Allos, B.M. and Ho, T. (1998) Campylobacter species and Guillain-BarreÂ syndrome. Clinical Microbiology Reviews 11, 555-567.
58. Nachamkin, I., Yang, X.H. and Stern, N.J. (1993) Role of Campylobacter jejuni flagella as colonization factors for three-day-old chicks: analysis with flagellar mutants. Applied and Environmental Microbiol- ogy 59, 1269-1273.
59. Newell, D.G., McBride, H. and Dolby, J.M. (1985) Investigations on the role of flagella in the colonization of infant mice with Campylobacter jejuni and attachment of Campylobacter jejuni to human epithelial cell lines. Journal of Hygiene 95, 217-227.
60. Nuijten, P.J.M., Bartels, C., Bleumink-Pluym, N.M.C., Gaastra, W. and van der Zeijst, B.A.M. (1990a) Size and physical map of the Campylobacter jejuni chromosome. Nucleic Acids Research 18, 6211-6214.
61. Nuijten, P.J.M., Marquez-Magana, L. and van der Zeijst, B.A.M. (1995) Analysis of flagellin gene expression in flagellar phase variants of Campylobacter jejuni 81116. Antonie Van Leeuwenhoek Interna- tional Journal of General and Molecular Microbiology 67, 377-383.

62. Nuijten, P.J.M., van Asten, F.J.A.M., Gaastra, W. and van der Zeijst, B.A.M. (1990b) Structural and functional analysis of two Campy- lobacter jejuni flagellin genes. Journal of Biological Chemistry 265, 17 798-17 804.

63. Oldfield, N.J. and Ketley, J.M. (1999) Organisation, gene content and variation of the major lipopolysaccharide cluster of C. jejuni NCTC 11168. In Abstracts 10th International Workshop on CHRO, Baltimore, MD. p. 75 (Abstract Cg6).

64. Pallen, M., Wren, B. and Parkhill, J. (1999) `Going wrong with confidence': misleading sequence analyses of CiaB and ClpX. Molecular Microbiology 34, 195.

65. Parkhill, J., Wren, B.W., Mungall, K., Ketley, J.M., Churcher, C., Basham, D., Chillingworth, T., Davies, R.M., Feltwell, T., Holroyd, S., Jagels, K., Karlyshev, A.V., Moule, S., Pallen, M.J., Penn, C.W., Quall, M.A., Rajandream, M.A., Rutherford, K.M., van Vliet, A.H.M., Whitehead, S. and Barrell, B.G. (2000) The genome sequence of the food-borne pathogen Campylobacter jejuni reveals hypervariable sequences. Nature 403, 665-668.

66. Parkinson, J.S. (1993) Signal transduction schemes of bacteria. Cell 73, 857-871.

67. Pei, Z., Burucoa, C., Grignon, B., Baqar, S., Huang, X.Z., Kopecko, D.J., Bourgeois, A.L., Fauchere, J.L. and Blaser, M.J. (1998) Mutation in the peb1A locus of Campylobacter jejuni reduces interactions with epithelial cells and intestinal colonization of mice. Infection and Immunity 66, 938-943.

68. Pesci, E.C., Cottle, D.L. and Pickett, C.L. (1994) Genetic, enzymatic, and pathogenic studies of the iron superoxide dismutase of Campylobacter jejuni. Infection and Immunity 62, 2687-2694.

69. Pickett, C.L., Auffenberg, T., Pesci, E.C., Sheen, V.L. and Jusuf, S.S. (1992) Iron acquisition and hemolysin production by Campylobacter jejuni. Infection and Immunity 60, 3872-3877.

70. Pickett, C.L., Pesci, E.C., Cottle, D.L., Russell, G., Erdem, A.N. and Zeytin, H. (1996) Prevalence of cytolethal distending toxin produc- tion in Campylobacter jejuni and relatedness of Campylobacter sp. cdtB gene. Infection and Immunity 64, 2070-2078.

71. Purdy, D., Buswell, C.M., Hodgson, A.E., McAlpine, K., Henderson, I. and Leach, S.A. (2000) Characterisation of cytolethal distending toxin (CDT) mutants of Campylobacter jejuni. Journal of Medical Microbiology 49, 473-479.

72. Purdy, D., Cawthraw, S., Dickinson, J.H., Newell, D.G. and Park, S.F. (1999) Generation of a superoxide dismutase (SOD)- deficient mutant of Campylobacter coli: Evidence for the significance of SOD in Campylobacter survival and colonization. Applied and Environmental Microbiology 65, 2540-2546.

73. Purdy, D. and Park, S.F. (1994) Cloning, nucleotide sequence and characterization of a gene encoding superoxide dismutase from Campylobacter jejuni and Campylobacter coli. Microbiology 140, 1203-1208.

74. Richardson, P.T. and Park, S.F. (1995) Enterochelin acquisition in Campylobacter coli: characterization of components of a binding- protein-dependent transport system. Microbiology 141, 3181-3191.

75. Rock, J.D., van Vliet, A.H.M. and Ketley, J.M. (1999) Characterisation of the haemin uptake system of Campylobacter jejuni. In Abstracts 10th International Workshop on CHRO, Baltimore, MD, p. 86 (Abstract Cp12).

76. Rollins, D.M. and Colwell, R.R. (1986) Viable but nonculturable stage of Campylobacter jejuni and its role in survival in the natural aquatic environment. Applied and Environmental Microbiology 52, 531-538.

77. Spohn, G. and Scarlato, V. (1999a) Motility of Helicobacter pylori is coordinately regulated by the transcriptional activator FlgR, an NtrC homolog. Journal of Bacteriology 181, 593-599.
78. Spohn, G. and Scarlato, V. (1999b) The autoregulatory HspR repressor protein governs chaperone gene transcription in Helico- bacter pylori. Molecular Microbiology 34, 663-674.
79. Stojiljkovic, I., Cobeljic, M. and Hantke, K. (1993) Escherichia coli K-12 ferrous iron uptake mutants are impaired in their ability to colonize the mouse intestine. FEMS Microbiology Letters 108, 111-115.
80. Storz, G. and Imlay, J.A. (1999) Oxidative stress. Current Opinions in Microbiology 2, 188-194.
81. Szymanski, C.M., King, M., Haardt, M. and Armstrong, G.D. (1995) Campylobacter jejuni motility and invasion of Caco-2 cells. Infection and Immunity 63, 4295-4300.
82. Szymanski, C.M., Yao, R., Ewing, C.P., Trust, T.J. and Guerry, P. (1999) Evidence for a system of general protein glycosylation in Campylobacter jejuni. Molecular Microbiology 32, 1022-1030.
83. Takata, T., Fujimoto, S. and Amako, K. (1992) Isolation of nonchemotactic mutants of Campylobacter jejuni and their coloniza- tion of the mouse intestinal tract. Infection and Immunity 60, 3596-3600.
84. Tauxe, R.V. (1992) Epidemiology of Campylobacter jejuni infections in the United States and other industrialized nations. In Campylobacter jejuni: Current Status and Future Trends ed. Nachamkin, I., Blaser, M.J. and Tompkins, L.S. pp. 9-19. Washington, DC: American Society for Microbiology.
85. Taylor, D.E. (1992) Genetics of Campylobacter and Helicobacter. Annual Reviews in Microbiology 46, 35-64.
86. Thies, F.L., Karch, H., Hartung, H.P. and Giegerich, G. (1999a) The ClpB protein from Campylobacter jejuni: molecular characterization of the encoding gene and antigenicity of the recombinant protein. Gene 230, 61-67.
87. Thies, F.L., Karch, H., Hartung, H.P. and Giegerich, G. (1999b) Cloning and expression of the dnaK gene of Campylobacter jejuni and antigenicity of heat shock protein 70. Infection and Immunity 67, 1194-1200.
88. Thies, F.L., Weishaupt, A., Karch, H., Hartung, H.P. and Giegerich, G. (1999c) Cloning, sequencing and molecular analysis of the Campylobacter jejuni groESL bicistronic operon. Microbiology 145, 89-98.
89. Tholozan, J.L., Cappelier, J.M., Tissier, J.P., Delattre, G. and Federighi, M. (1999) Physiological characterization of viable-but- nonculturable Campylobacter jejuni cells. Applied and Environmental Microbiology 65, 1110-1116.
90. Velayudhan, J., Hughes, N.J., McColm, A.A., Bagshaw, J., Clayton, C.L., Andrews, S.C. and Kelly, D.J. (2000) Iron acquisition and virulence in Helicobacter pylori: a major role for FeoB, a high-affinity ferrous iron transporter. Molecular Microbiol- ogy 37, 274-286.
91. van Vliet, A.H.M., Baillon, M.L.A., Penn, C.W. and Ketley, J.M. (1999) Campylobacter jejuni contains two Fur homologs: Characterization of iron-responsive regulation of peroxide stress defence genes by the PerR repressor. Journal of Bacteriology 181, 6371-6376.
92. van Vliet, A.H.M., Baillon, M.L.A., Penn, C.W. and Ketley, J.M. (2001) The iron-induced terradoxin FdxA of Campylobacter jejuni is involved in aerotolerance. FEMS Microbiology Letters 196, 189-193.
93. van Vliet, A.H.M., Rock, J.D., Madeleine, L.N. and Ketley, J.M. (2000) The iron responsive regulator Fur of Campylobacter jejuni is expressed from two separate promoters. FEMS Microbiology Letters 188, 115-118.
94. van Vliet, A.H.M., Wood, A.C., Henderson, J., Wooldridge, K.G. and Ketley, J.M. (1998a) Genetic manipulation of enteric Campylobacter species. Methods in Microbiology 27, 407-419.

95. van Vliet, A.H.M., Wooldridge, K.G. and Ketley, J.M. (1998b) Iron- responsive gene regulation in a Campylobacter jejuni fur mutant. Journal of Bacteriology 180, 5291-5298.
96. Whitehouse, C.A., Balbo, P.B., Pesci, E.C., Cottle, D.L., Mirabito, P.M. and Pickett, C.L. (1998) Campylobacter jejuni cytolethal distending toxin causes a G2-phase cell cycle block. Infection and Immunity 66, 1934-1940.
97. Wang, Y. and Taylor, D.E. (1990) Natural transformation in Campylobacter species. Journal of Bacteriology 172, 949-955.
98. Wassenaar, T.M. (1997) Toxin production by Campylobacter. Clinical Microbiology Reviews 10, 466-476.
99. Wassenaar, T.M., Bleumink-Pluym, N.M.C., Newell, D.G., Nuijten, P.J. and van der Zeijst, B.A.M. (1994) Differential flagellin expression in a flaA flaB+ mutant of Campylobacter jejuni. Infection and Immunity 62, 3901-3906.
100. Wassenaar, T.M., Bleumink-Pluym, N.M.C. and van der Zeijst, B.A.M. (1991) Inactivation of Campylobacter jejuni flagellin genes by homologous recombination demonstrates that flaA but not flaB is required for invasion. EMBO Journal 10, 2055-2061.
101. Wood, A.C., Oldfield, N.J., O'Dwyer, C.A. and Ketley, J.M. (1999) Cloning, mutation and distribution of a putative lipopolysaccharide biosynthesis locus in Campylobacter jejuni. Microbiology 145, 379-388.
102. Wooldridge, K.G. and Ketley, J.M. (1997) Campylobacter-host cell interactions. Trends in Microbiology 5, 96-102.
103. Wooldridge, K.G., Williams, P.H. and Ketley, J.M. (1994) Iron responsive genetic regulation in Campylobacter jejuni: cloning and characterization of a fur homolog. Journal of Bacteriology, 176, 5852-5856.
104. Wooldridge, K.G., Williams, P.H. and Ketley, J.M. (1996) Host signal-transduction and endocytosis of Campylobacter jejuni. Micro- bial Pathogenesis 21, 299-305.
105. Wosten, M.M.S.M., Boeve, M., Gaastra, W. and van der Zeijst, B.A.M. (1998) Cloning and characterization of the gene encoding the primary sigma-factor of Campylobacter jejuni. FEMS Microbiology Letters 162, 97-103.
106. Wosten, M.M.S.M., Ishiguro, E.E. and van der Zeijst, B.A.M. (1997) Cloning and characterization of the lytB gene of Campylobacter jejuni. FEMS Microbiology Letters 157, 117-121.
107. Wren, B.W., Colby, S.M., Cubberley, R.R. and Pallen, M.J. (1992) Degenerate PCR primers for the amplification of fragments from genes encoding response regulators from a range of pathogenic bacteria. FEMS Microbiology Letters 78, 287-291.
108. Yao, R., Burr, D.H., Doig, P., Trust, T.J., Niu, H. and Guerry, P. (1994) Isolation of motile and non-motile insertional mutants of Campylobacter jejuni: the role of motility in adherence and invasion of eukaryotic cells. Molecular Microbiology 14, 883-893.
109. Yao, R., Burr, D.H. and Guerry, P. (1997) CheY-mediated modulation of Campylobacter jejuni virulence. Molecular Microbiology 23, 1021-1031.
110. Ziprin, R.L., Young, C.R., Stanker, L.H., Hume, M.E. and Konkel, M.E. (1999) the absence of cecal colonization of chicks by a mutant of Campylobacter jejuni not expressing bacterial fibronectin-binding protein. Avian Diseases 43, 586-589.

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