

PATHOPHYSIOLOGY OF ENTERIC INFECTIONS WITH *GIARDIA DUODENALIS*

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Summary:

Giardia is the most prevalent human intestinal parasitic protist in the world, and one of the most common parasite of companion animals and young livestock. *Giardia* is a major cause of diarrhea in children and in travelers. The host-microbial interactions that govern the outcome of infection remain incompletely understood. Findings available to date indicate that the infection causes diarrhea via a combination of intestinal malabsorption and hypersecretion. Malabsorption and maldigestion mainly result from a diffuse shortening of epithelial microvilli. This enterocytic injury is mediated by activated host T lymphocytes. Pathophysiological activation of lymphocytes is secondary to *Giardia*-induced disruption of epithelial tight junctions, which in turn increases intestinal permeability. Loss of epithelial barrier function is a result of *Giardia*-induced enterocyte apoptosis. Recent findings suggest that these effects may facilitate the development of chronic enteric disorders, including inflammatory bowel disease, irritable bowel syndrome, and allergies, via mechanisms that remain poorly understood. A newly discovered SGLT-1 glucose uptake-mediated host cytoprotective mechanism may represent an effective modulator of the epithelial apoptosis induced by this parasite, and, possibly, by other enteropathogens. A better understanding of the pathogenesis of giardiasis will shed light on new potential therapeutic targets.

KEY WORDS : *Giardia*, intestinal pathophysiology, apoptosis, diarrhea, proteases, irritable bowel syndrome, inflammatory bowel disease.

Giardiasis is the most common protozoan infection of the human small intestine. The high prevalence of infection with *Giardia duodenalis* (syn. *lamblia*, *intestinalis*) has earned this cosmopolitan parasite a spot on the World Health Organization's "Neglected Diseases Initiative" (Savioli *et al.*, 2006). Ample evidence suggests that *Giardia*, which has been found in all classes of vertebrates examined to date, has great potential for zoonotic transmission (Caccio *et al.*, 2005). Various *Giardia* genotypes have been identified, with assemblages A and B being infectious to humans (Wielinga & Thompson, 2007). Infection with this non-invasive entero-pathogen may cause diarrhea, dehydration, abdominal discomfort, malabsorption and weight loss. Symptoms can be present in the absence of any significant morphologic injury to the intestinal

mucosa, and infections may remain asymptomatic or become chronic for reasons that remain obscure (Faubert, 2000; Eckmann *et al.*, 2001; Buret *et al.*, 2002; Mueller & von Allmen, 2005; Gascon, 2006; Roxstrom-Lindquist *et al.*, 2006). Variable expression of *Giardia* surface proteins may help the parasite to evade host immunity (Faubert, 2000; Roxstrom-Lindquist *et al.*, 2006). The epithelial abnormalities responsible for intestinal malabsorption and diarrhea in giardiasis share similarities with those observed in other enteric disorders, such as bacterial enteritis (Buret *et al.*, 1990, 1998), chronic food anaphylaxis (Curtis *et al.*, 1990), inflammatory bowel disease disease (Gunasekaran & Hassal, 1992), and celiac disease (Rubin *et al.*, 1966). Therefore, a better understanding of the pathophysiological processes implicated in giardiasis may help unravel mechanisms responsible for a variety of intestinal diseases. The recent publication of the *Giardia duodenalis* genome contained in the 5 chromosomes of this parasite will facilitate our search towards novel therapeutic strategies (Morrison *et al.*, 2007).

MECHANISMS OF HEIGHTENED ENTEROCYTIC APOPTOSIS AND ANTI-APOPTOTIC RESCUE

Studies *in vitro* have established that *Giardia duodenalis* may induce enterocytic apoptosis in strain-dependent fashion (Chin *et al.*, 2002). Intriguingly, this effect, and the resulting disruption of tight junctional integrity, can be inhibited with apical administration of epidermal growth factor (Buret *et al.*, 2002). The potential therapeutic significance of this observation requires further clarification. Findings from microarray analyses on the effects of *G. duodenalis* on human CaCo2 cells found that the parasite-host interactions lead to a significant upregulation of genes implicated in the apoptotic cascade and the formation of reactive oxygen species (Roxstrom-Lindquist *et al.*, 2005). Consistent with these observations, a recent report demonstrated that *Giardia*-induced apoptosis in human epithelial cells involves caspase-3 activation, PARP

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cleavage, down-regulation of anti-apoptotic Bcl-2, and increased expression of pro-apoptotic Bax (Panaro *et al.*, 2007). Studies in human patients with chronic giardiasis have now confirmed that infection with *Giardia duodenalis* is indeed associated with increased rates of enterocyte apoptosis (Troeger *et al.*, 2007). *Giardia* can also prevent the formation of epithelial nitric oxide, a compound known to inhibit giardial growth, by consuming local arginine, which effectively removes the substrate needed by enterocytes to produce nitric oxide (Eckmann *et al.*, 2000). This mechanism may contribute to *Giardia*-induced enterocyte apoptosis, since arginine starvation in these cells is known to cause programmed cell death (Potoka *et al.*, 2003). A broad variety of enteropathogens are known to cause epithelial apoptosis. Recent reports described a novel biological process in which sodium-coupled-glucose transporter-1 (SGLT-1) activation may rescue enterocytes from lipopolysaccharide-induced epithelial cell apoptosis by enhancing glucose uptake (Yu *et al.*, 2005, 2006). The intriguing possibility that this mechanism may represent a hitherto unreported generic host defense process to promote cell survival against pro-apoptotic enteropathogens, including *Giardia*, is a topic of ongoing research (Yu *et al.*, 2008).

LOSS OF EPITHELIAL BARRIER FUNCTION

Immune or drug-induced enterocyte apoptosis may cause a loss of intestinal epithelial barrier function (Sun *et al.*, 1998; Abreu *et al.*, 2000; Bojarski *et al.*, 2000; Gitter *et al.*, 2000). These observations have prompted studies into the effects of *Giardia*-induced apoptosis on epithelial permeability. Observations from models *in vitro* and *in vivo* have established that *Giardia* parasites increase intestinal permeability (Scott *et al.*, 2002). Moreover, infection with *Giardia duodenalis* in gerbils has been associated with elevated macromolecular uptake in the jejunum during the period of peak trophozoite colonization, but not during the parasite clearance phase (Hardin *et al.*, 1997). It was recently demonstrated that chronic giardiasis is also responsible for a loss of intestinal barrier function in human infections (Troeger *et al.*, 2007). Increased epithelial permeability allows luminal antigens to activate host immune-dependent pathological pathways. Therefore, such events may be of great clinical significance. Not surprisingly, intense research efforts are trying to identify the molecular events regulating epithelial tight junctional function in gastrointestinal health and in disease (Laukoetter *et al.*, 2006; Shen *et al.*, 2006). In giardiasis, disruptions of cellular F-actin and tight junctional ZO-1, as well as the resulting increase in trans-epithelial permeability, appear to be modulated at least in part by myosin-light-chain kinase and pro-apoptotic

caspase-3 (Chin *et al.*, 2002; Scott *et al.*, 2002). Other studies also found that *Giardia* disrupts enterocyte alpha-actinin, a component of the actomyosin ring that regulates paracellular flow across intestinal epithelia (Teoh *et al.*, 2000). Consistent with these observations, the parasite also affects epithelial claudin proteins, which are critical components of the sealing properties of tight junctions; these alterations have been shown to disrupt intestinal barrier function in human giardiasis (Troeger *et al.*, 2007). Together, the findings available to date indicate that *Giardia*-induced enterocyte apoptosis is responsible for increased intestinal permeability during the infection. The cytosolic trafficking pathways involved in the *Giardia*-induced alterations to tight junctional proteins have yet to be uncovered.

SHORTENING OF EPITHELIAL MICROVILLI AND TRANSPORT ABNORMALITIES

Symptoms during giardiasis may occur in the absence of overt villus atrophy or other signs of mucosal injury (Eckman *et al.*, 2001; Mueller & von Allmen, 2005; Gascon, 2006; Roxstrom-Lindquist *et al.*, 2006). These observations have prompted investigations into the mechanisms responsible for intestinal dysfunction during giardiasis. Studies using models *in vivo* and *in vitro*, as well as recent observations from humans infected with this parasite, have established that *Giardia duodenalis* causes malabsorption of glucose, sodium, and water, and reduced disaccharidase activity; malabsorption and maldigestion are due to a diffuse shortening of epithelial microvilli (Belosevic *et al.*, 1989; Buret *et al.*, 1992; Cevallos *et al.*, 1995; Troeger *et al.*, 2007). This parasite may also induce chloride secretion in human colonic cells *in vitro*, in murine models of infection, as well as in human patients (Gorowara *et al.*, 1992; Resta-Lenert *et al.*, 2000; Troeger *et al.*, 2007). Therefore, during this infection, a combination of malabsorption and hypersecretion of electrolytes seems to be responsible for fluid accumulation in the intestinal lumen, which in turn leads to diarrhea. The mechanisms responsible for these abnormalities remain unclear. Increased numbers of intra-epithelial lymphocytes are associated with the sodium/glucose malabsorption detected in human patients infected with *Giardia duodenalis* (Troeger *et al.*, 2007). Consistent with a pathophysiological role of subepithelial immune activation secondary to a breach in the epithelial barrier, epithelial brush border injury and disaccharidase deficiencies in giardiasis appear to be mediated by CD8+ T cells (Scott *et al.*, 2004). Indeed, microvillus brush border abnormalities are not observed in hosts devoid of functional T lymphocytes, despite the presence of live parasites (Scott *et al.*, 2000). These obser-

vations refute the hypothesis that intestinal malfunction in giardiasis simply results from trophozoite attachment or parasite virulence factors. Instead, parasite products may break the epithelial barrier, following which activated T lymphocytes cause the brush border to retract, which in turn leads to disaccharidase deficiencies and epithelial malabsorption, ultimately causing diarrhea.

POST-GIARDIASIS CHRONIC INTESTINAL DISTURBANCES

Enteropathogens have been implicated in the pathogenesis of a variety of chronic disorders of the gastrointestinal tract including food allergy, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS). Indeed, acute microbial infections may directly be responsible for relapse in IBD (Weber *et al.*, 1992; Rodriguez *et al.*, 2006). Similarly, acute exposure to bacterial enteropathogens has been associated with post-infectious irritable bowel syndrome (Thornley *et al.*, 2001; Marshall *et al.*, 2006). While these and other studies suggest that inflammation can be induced in susceptible hosts by a simple loss of epithelial barrier integrity, the mechanisms implicated remain poorly understood. As this association seems to be conserved across the global distribution of these disorders, the possible pathogenic role for cosmopolitan microbes, including *Giardia*, needs to be investigated. Tight junctional integrity plays a central role in allowing the host to discriminate between pathogens and commensal bacteria. Factors inducing a change in epithelial polarity, or a disruption of tight junctional complexes, may permit luminal material, including commensal bacteria and/or their products, to activate baso-lateral immune "sensors" which otherwise may have remained inaccessible (eg. TLR's). Therefore, luminal factors capable of breaching epithelial integrity may predispose the intestine to heightened intestinal inflammation in susceptible patients. Whether and how acute or chronic infection with *Giardia duodenalis* may be implicated in the initiation and/or exacerbation of chronic intestinal inflammation by contributing to such epithelial alterations remains unclear. A recent report demonstrated that *Giardia* may elicit symptoms similar to IBS (D'Anchino *et al.*, 2002). Moreover, giardiasis has been associated with various types of allergic symptoms (Clyne & Eliopoulos, 1989; Di Prisco *et al.*, 1993). In giardiasis, mast cell hyperplasia follows infection-induced loss of intestinal barrier function (Hardin *et al.*, 1997). The mechanisms whereby infection may exacerbate a clinically silent IBD, and/or initiate diseases such as IBS and allergy, warrant further investigation. The implications of microbially-induced intestinal "leakage" in these disorders represent important topics for future research.

CONCLUSION

The mechanisms by which *Giardia* causes diarrhea are multifactorial, and include parasite-induced chloride hypersecretion, epithelial apoptosis and loss of barrier function, leading to lymphocyte-mediated microvillous shortening and reduction of absorptive surface area, which ultimately are responsible for maldigestion and malabsorption of nutrients, sodium, and water. These processes seem to be strain-dependent, but the pathogenic significance of the various genotypes known to exist has yet to be established. Similarly, the pathogenic role of parasite products such as surface glycoproteins, lectins, proteinases or other types of "enterotoxins" still requires further clarification, but evidence indicates that activation of epithelial proteinase-activated receptors alone may elicit caspase-dependent epithelial barrier disruptions, in a manner reminiscent of the direct effects of the parasite. Finally, recent evidence indicates that infection-associated loss of epithelial barrier function may lead to chronic intestinal disorders *via* mechanisms that remain obscure. The ever-increasing number of studies reporting new developments in the field, together with the completion of the *Giardia* genome project, will help develop new prophylactic and therapeutic measures against this important intestinal infection, and possibly against the chronic enteric diseases it has been associated with.

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