RESEARCH ARTICLE

Differential protein abundance of a basolateral MCT1 transporter in the human gastrointestinal tract

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Abstract

Bacterially derived short chain fatty acids (SCFAs), such as butyrate, are vital in maintaining the symbiotic relationship that exists between humans and their gastrointestinal microbial populations. A key step in this process is the transport of SCFAs across colonic epithelial cells via MCT1 transporters. This study investigated MCT1 protein abundance in various human intestinal tissues. Initial RT-PCR analysis confirmed the expected MCT1 RNA expression pattern of colon > small intestine > stomach. Using surgical resection samples, immunoblot analysis detected higher abundance of a 45 kDa MCT1 protein in colonic tissue compared to ileum tissue ($P < 0.001$, $N = 4$, unpaired t-test). Importantly, MCT1 abundance was found to be significantly lower in sigmoid colon compared to ascending colon ($P < 0.01$, $N = 8–11$, ANOVA). Finally, immunolocalization studies confirmed MCT1 to be abundant in the basolateral membranes of surface epithelial cells of the ascending, transverse, and descending colon, but significantly less prevalent in the sigmoid colon ($P < 0.05$, $N = 5–21$, ANOVA). In conclusion, these data confirm that basolateral MCT1 protein abundance is correlated to levels of bacterially derived SCFAs along the human gastrointestinal tract. These findings highlight the importance of precise tissue location in studies comparing colonic MCT1 abundance between normal and diseased states.

Keywords: colon; immunolocalization; MCT1; protein abundance

Introduction

Short chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, are produced by bacterial fermentation processes that take place within the human gastrointestinal tract (Topping and Clifton, 2001). These bacterially derived SCFAs are vital in maintaining the symbiotic relationship between humans and their gastrointestinal microbial populations, particularly in the colon. Importantly, the SCFAs can either be used locally by epithelial cells lining the intestinal tract, or reabsorbed transcellularly across the epithelial barrier and into the bloodstream (Tan et al., 2014). For example, healthy human colonocytes obtain around 60–70% of their energy from SCFAs (Lambert et al., 2002). A key step in these processes is the uptake and transport of SCFAs into and out of intestinal epithelial cells via monocarboxylate transporters (MCTs), such as MCT1 and MCT4 (Gill et al., 2005).

MCT1 is one of the most important transporters involved in the uptake of bacterially derived SCFAs. Originally, MCT1 mRNA and protein were detected in the human colon (Ritzhaupt et al., 1998). Further studies showed that butyrate increased mRNA and protein expression of MCT1, whereas neither acetate nor propionate had any effect (Cuff et al., 2002). It is now known that butyrate stimulates MCT1 promoter activity (Borthakur et al., 2008), with substrate-induced enhancement of MCT1 surface expression through a novel nutrient sensing mechanism involving the GPR109A receptor as a SCFA sensor (Borthakur et al., 2012). Indeed, MCT1 is vital to butyrate regulation of colonocyte cell cycle arrest and differentiation (Cuff et al., 2005) and is hence believed to play a key role in human colonic health.

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In agreement with this butyrate-regulated expression, MCT1 mRNA and protein have predominantly been reported in the region of the human gastrointestinal tract where bacterial populations are most abundant, namely the colon. Nevertheless, the exact cellular localization of MCT1 protein remains controversial. Initially, MCT1 protein was reported to be situated on the apical membrane of colonic epithelial cells (Ritzhaupt et al., 1998), with greater abundance in the distal compared to proximal colon (Gill et al., 2005). However, in a contrasting study, MCT1 protein has also been reported in the basolateral membranes of colonic surface epithelial cells, with an expression pattern of proximal colon > sigmoid colon > rectum (Iwanaga et al., 2006). The aim of this study was, therefore, to precisely determine MCT1 protein abundance in various intestinal tissues, particularly different regions of the colon, to clarify the localization of the MCT1 transporter within the human gastrointestinal tract.

Methods

RT-PCR

Using purchased mRNA samples (AMS Biotechnology, UK), cDNA preparation was performed using a Go-Script reverse transcription kit (Medical Supply Company, Ireland). Resulting cDNA samples underwent PCR amplification with a Platinum Taq polymerase enzyme (Biosciences Ltd., Ireland), using MCT1, CD147, or PepT1 primers. Primer sequences were MCT1 forward = 5'-ATTGGAG-GTCTTGCGTTGC-3', MCT1 reverse = 5'-CATTCCA-CAATGGTCAACCA-3'; CD147 forward = 5'-GCAGGT-TCTCTGAGTTCC-3', CD147 reverse = 5'-GCCTTTG-TCATTCTGTTGCT-3'; PepT1 forward = 5'-TTCCA-CAATCATCACACC-3', PepT1 reverse = 5'-AACATCACC-CCTGTAACC-3'. Cycling parameters were initial denaturation 94°C for 2 min, followed by 30 or 35 cycles at 94°C for 30 s, 55°C or 60°C for 30 s, and 72°C for 30 s. The final extension was at 72°C for 5 min. Identity of PCR products were confirmed through direct sequencing (Eurofins MWG, Operon, Germany). Control PCR experiments using actin and GAPDH primers were also performed to confirm cDNA sample integrity.

Tissue source and ethical approval

Human ileum and colon were obtained at surgical resection for carcinoma. The normal histological appearance of tissues was confirmed by routine pathological examination of samples obtained during dissection. Tissues from resection margins were immediately transferred to the laboratory in preoxygenated Krebs-Henseleit (KH) solution (composition in mM; 118 NaCl, 4.7 KCl, 2.5 CaCl$_2$, 1.2 MgSO$_4$, 1.2 KH$_2$PO$_4$, 25 NaHCO$_3$, and 11.1 D-glucose, pH 7.4). St. Vincent’s University Hospital Institutional Review Board Approval (including informed patient consent) was granted for this study.

Antibodies

To study the distribution of human MCT1, we utilized two different commercial anti-MCT1 polyclonal antibodies (MCT12A, Alpha Diagnostics, UK; AB3538P, Millipore, UK). To detect PepT1 transporter protein, we utilized the polyclonal anti-PepT1 antibody (H235-PEPT1, Santa Cruz Biotechnology, Inc., USA). In addition, commercial monoclonal antibodies were used to detect CD147 (sc-21746, Santa Cruz Biotechnology, Inc., USA), actin (sc-1615, Santa Cruz Biotechnology, Inc., USA), and GAPDH (Y3322GAPDH, AMS Biotechnology, UK). Horse radish peroxidase conjugated secondary antibodies raised were also utilized: anti-rabbit IgG (65–6120, Invitrogen, USA), anti-goat (61–1620, Invitrogen, USA), and anti-mouse (61–6520, Invitrogen, USA).

Immunoblotting

Initial experiments were performed using purchased whole cell homogenate samples of stomach, small intestine, cecum, and colon (AMS Biotechnology, UK). All remaining experiments utilized protein prepared from human ileum and colon resection tissues. These human samples were homogenized with an automated homogenizer and a specifically prepared homogenization buffer (300 mM mannitol, 12 mM HEPES, pH 7.6). Homogenates were spun at 2,500 g at 4°C for 5 min and the pelletted cellular debris removed to leave the whole cell homogenate. This homogenate was then further spun at 17,000 g at 4°C for 30 min, producing a pellet of plasma membrane-enriched protein which was retained and resuspended in fresh homogenization buffer. The remaining supernatant represented cytosolic-enriched protein and was also retained. For deglycosylation experiments, colonic protein samples were treated with PNGaseF enzyme (New England Biolabs, USA) for 1 h at 37°C. For loading onto western gels, 2X reducing Laemmli sample buffer (5% SDS, 25% glycerol, 0.32 M Tris, pH 6.8, bromophenol blue, and 5% β-mercaptoethanol) was added to protein samples in a ratio of 1:1 and the mixture heated at 70°C for 15 min. SDS-PAGE was performed on minigels of 12% polyacrylamide by loading ~15 μg protein per lane. After transfer to nitrocellulose membranes, immunoblots were probed for either 1 or 16 h at room temperature in 1:1,000 primary antibody (MCT12A, AB3538P, H235-PEPT1, CD147, actin, or GAPDH). Immunoblots were then washed and probed with 1:5,000 of the relevant horse radish.
peroxidase-conjugated secondary antibody (either anti-rabbit, anti-goat, or anti-mouse) for 1 h at room temperature. After further washing, detection of protein was performed using Western Lightning Plus ECL reagents (Perkin Elmer, UK) and a LAS-4000 Image Reader (Fujifilm, Japan). Finally, densitometry analysis of the resulting immunoblot images was performed using ImageJ software (National Institute of Health, USA).

Immunolocalization

Paraffin-embedded tissue sections (AMS Biotechnology, UK) and microarray slides (Novus Biologicals, UK) were purchased and used for immunolocalization studies. After Neo-Clear™ treatment and rehydration in a descending series of ethanol concentrations (100–70%), endogenous peroxidase was blocked by incubating sections for 30 min in 3% hydrogen peroxide in methanol. Antigen retrieval was performed by boiling sections for 5 min in a solution containing 25 mM Tris–HCl (pH 8.0) and 10 mM EDTA, before overnight incubation at 4°C with 1:250 dilution of primary antibody (MCT12A or AB3538P) diluted in 0.1% BSA and 0.3% Triton X-100 in PBS. Labeling was visualized with a 1:200 dilution of horseradish peroxidase-conjugated secondary antibody (anti-rabbit), followed by incubation with diaminobenzidine and counterstaining with hematoxylin. Stained sections were then dehydrated in an ascending series of ethanol concentrations (70–100%), treated with Neo-Clear™ and coverslips mounted using Eukitt mounting medium.

Figure 1 Analysis of MCT1 along the human gastrointestinal tract. (A) RT-PCR experiments detected the expected 840 bp MCT1 product in both small intestine and colon samples. In contrast, PepT1 primers detected the predicted 300 bp signal only in the small intestine. Primers for CD147, GAPDH, and actin all detected strong signals in stomach, small intestine, and colon samples. Key: RT = reverse transcription; + = with enzyme; – = without enzyme; St = stomach; SI = small intestine; Co = colon. (B) Immunoblotting analysis using whole cell homogenates (25 μg per lane) showed strong signals for both MCT1 and CD147 in cecum and colon, but not stomach or small intestine. Strong 38 kDa signals representing GAPDH were detected in all four samples. Key: df = dye front. (C) Strong immunoblot staining for MCT1 and CD147 was obtained in membrane-enriched but not cytosolic-enriched colonic protein samples (10 μg per lane). In contrast, strong actin and GAPDH signals were obtained in both protein samples. (D) Deglycosylation induced by treatment with PNGaseF enzyme shifted 45–60 kDa colonic CD147 signals to 34 and 40 kDa proteins, but had no effect on 38 kDa GAPDH protein.
Immunofluorescent staining

Frozen human transverse colon 5 μm sections (AMS Biotechnology, UK) were stained using an anti-MCT1 antibody (AB3538P, 1:200 dilution) and detected using an AlexaFluor 568 labeled secondary antibody, whilst nuclei were stained using Hoechst 33342. Control tissue staining was performed by omitting the primary antibody. Representative images were acquired using a Leica DMI6000B wide-field inverted microscope with a 20X objective.

Statistical analysis

Data are shown as mean ± SEM (standard error mean), with N representing the number of samples. Unpaired t-tests or one-way ANOVA were used as appropriate. Groups were deemed statistically significant if P < 0.05, and ANOVA was performed using the Tukey post hoc test (Instat, GraphPad Software).

Results

RT-PCR experiments were performed to investigate RNA expression in human stomach, small intestine, and colon (Figure 1A). The expected 840 bp MCT1 transporter signal was strongly detected in the colon, but also more weakly in the small intestine. In contrast, the peptide transporter PepT1 signal was only expressed in small intestine, while strong signals for CD147, GAPDH, and actin were detected in all three samples. The identity of all five products was confirmed by direct sequencing (data not shown). No signals were detected in any of the RT control samples. Next, in order to investigate whether protein abundance matched the RNA expression patterns suggested by RT-PCR, immunoblot analysis was performed using purchased human whole homogenate protein samples. Initial analysis using these homogenates suggested MCT1 and CD147 proteins were abundant in cecum and colon samples, but not in the stomach or small intestine (Figure 1B). Using protein samples prepared from colonic resection tissues, further experiments showed strong 45 kDa MCT1 and 40–60 kDa CD147 signals were present in membrane-enriched protein, but not cytosolic-enriched protein (Figure 1C). In contrast, 43 kDa actin and 38 kDa GAPDH signals were strongly detected in both membrane- and cytosolic-enriched samples. Finally, deglycosylation experiments confirmed that the 45–60 kDa CD147 signal shifted to core proteins of 34 and 40 kDa in size, while 38 kDa GAPDH protein was totally unaffected (Figure 1D).

Following these initial exploratory experiments, comparison of transporter protein abundance was then performed using a number of non-matched ileum and colon samples (Figure 2A). The resulting immunoblots showed the expected 45 kDa MCT1 signal was strongly detected in the colon, while 45–60 kDa glycosylated CD147 protein was also detected strongly in colon and weakly in ileum. In contrast, a 100 kDa PepT1 protein signal was only found in ileum. There was no statistical difference in actin signals obtained in ileum and colon samples. Densitometry analysis of all these immunoblots showed significantly higher abundance of both MCT1 and CD147 in colon samples, whereas PepT1 expression was higher in ileum. There was no statistical difference in actin signals obtained in ileum and colon samples. Key: *P < 0.05, unpaired t-test; ***P < 0.001, unpaired t-test.
colonic compared to ileum samples. In contrast, PepT1 expression was significantly higher in the ileum \(P < 0.05, N = 4, \text{unpaired t-test}\), while there was no statistical difference in actin signals obtained in the two tissues (NS, \(N = 4, \text{unpaired t-test}\)) (Figure 2B).

In order to investigate the precise cellular location of MCT1, immunolocalization experiments were performed. Using MCT12A, no significant staining was observed in purchased 10 \(\mu\)m sections of either stomach or ileum (Figures 3A and 3B). In contrast, strong staining was obtained in colonic surface epithelial cells with the MCT1 antibodies, MCT12A (Figure 3C) and AB3538P (Figure 3D). In both cases, higher magnification images revealed this staining was predominantly in the basolateral membranes of these colonic epithelial cells (Figures 3E and 3F). Furthermore, this predominantly basolateral localization of MCT1 within surface epithelial cells was confirmed using immunofluorescent staining of frozen colon sections and widefield microscopy (Figure 4).

The next set of experiments were performed to determine whether MCT1 transporter abundance varied between different colonic regions. Firstly, again using cDNA samples prepared from purchased RNA samples, RT-PCR experiments suggested that MCT1 was strongly expressed in ascending colon, but only weakly expressed in sigmoid colon (Figure 5A). In contrast, strong signals for both CD147 and actin were observed in each tissue. Next, while strong 45 kDa MCT1 protein signals were detected in ascending colon samples, only weak signals were present in sigmoid colon samples (Figure 5B). No such difference was evident for either CD147 or actin protein. Importantly, densitometry analysis confirmed that there was a significant reduction of MCT1 protein abundance in sigmoid colon compared to ascending colon samples \(P < 0.01, N = 8\text{–}11, \text{ANOVA}\), but

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Figure 3 Immunolocalization of MCT1 protein along the human gastrointestinal tract. Using 1:250 MCT12A, no significant staining was detected in either (A) stomach \([\times 10 \text{ magnification lens}]\) or (B) ileum \([\times 10 \text{ magnification lens}]\). In contrast, strong MCT1 staining was obtained in colonic surface epithelial cells with (C) MCT12A \([\times 10 \text{ magnification lens}]\) and another MCT1 antibody (D) AB3538P \([\times 10 \text{ magnification lens}]\). Finally, this colonic surface epithelial staining was predominantly basolateral in nature as shown by higher magnification images for (E) MCT12A \([\times 20 \text{ magnification lens}]\), and (F) AB3538P \([\times 20 \text{ magnification lens}]\). All scale bars represent 100 \(\mu\)m.
**Figure 4** Immunofluorescent staining of MCT1 localization in human transverse colon. (A) Frozen colon tissue sections were stained with an anti-MCT1 antibody (1:200 AB3538P) and detected using an AlexaFluor 568 secondary antibody (Red), while nuclei were counterstained using Hoechst 33342 (Blue). (B) Control frozen colon tissue stained with AlexaFluor 568 secondary antibody only, and counterstained with Hoechst 3342 (Blue). Magnification 20×; scale bar, 100 μm; L indicates position of the colonic lumen, while arrowhead indicates position of the basolateral membrane.

**Figure 5** Analysis of MCT1 transporter abundance in different colonic regions. (A) RT-PCR experiments detected the expected 840 bp MCT1 product strongly in the ascending colon, but only weakly in sigmoid colon. In contrast, CD147 and actin were detected strongly in both samples. Key: RT = reverse transcription; + = with enzyme; − = without enzyme; Asc = ascending colon; Sig = sigmoid colon. (B) Immunoblot comparison of MCT1, CD147, and actin abundance in different regions of colon. Key: A = ascending colon; D = descending colon; S = sigmoid colon. (C) Densitometry analysis of immunoblot data showed reduced 45 kDa MCT1 protein abundance in sigmoid colon compared to ascending colon. No such difference was observed for either CD147 or actin. Key: **P < 0.01, ANOVA.
no such change was observed for CD147 or actin (NS, N = 7–8, ANOVA) (Figure 5C).

Finally, to further investigate the cellular localization of regional colonic MCT1 protein, extensive immunolocalization studies were performed using colonic tissue microarrays and AB3538P. These studies confirmed strong MCT1 protein detection in human ascending, transverse, and descending colon (Figures 6A–6C). MCT1 was mainly detected in the surface epithelial cells, particularly in the basolateral membranes. In contrast, little or no MCT1 staining was detected in the sigmoid colon (Figure 6D). Significant staining of red blood cells was obtained with AB3538P in each tissue section, regardless of the extent of MCT1 staining of the epithelial layer observed. Finally, scoring of epithelial MCT1 immunostaining in multiple colonic sections was performed blind by two researchers independently and mean score data compiled on the basis of colonic region (Table 1). These data confirmed significant differences in the MCT1 abundance along the human colon, again showing a reduced MCT1 abundance in the sigmoid colon (P < 0.05, N = 5–21, ANOVA).

Discussion

In the present study, we investigated the abundance of the SCFA transporter MCT1 in various human intestinal tissues. As expected, preliminary RT-PCR analysis suggested that MCT1 RNA expression was highest in the colon, followed by the small intestine and stomach. Immunoblotting detected higher abundance of MCT1 protein in colon compared to ileum. Furthermore, MCT1 abundance was found to be significantly higher in ascending colon compared to sigmoid colon. Finally, immunolocalization studies showed that MCT1 in ascending, transverse, and descending colon was mainly located in the basolateral membranes of the surface epithelial cells, whereas it was largely absent from the sigmoid colon.

Table 1 Summary of MCT1 immunostaining scores from different human colonic regions. *Blind* scoring of numerous MCT1-stained colonic sections was performed independently by two separate individual researchers. The mean scores were then calculated for each section of the human colon (mean ± SE). Scoring key: 0 = no staining; 1 = weak MCT1 staining; 2 = moderate MCT1 staining; 3 = strong MCT1 staining.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>AB3538P immunolocalization score</th>
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<tr>
<td>Ascending colon (N = 16)</td>
<td>0.80 ± 0.26</td>
</tr>
<tr>
<td>Transverse colon (N = 7)</td>
<td>1.29 ± 0.47</td>
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<tr>
<td>Descending colon (N = 5)</td>
<td>0.80 ± 0.49</td>
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<tr>
<td>Sigmoid colon (N = 21)</td>
<td>0.14 ± 0.10</td>
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<td>ANOVA</td>
<td>P = 0.0175</td>
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It is known that SCFA concentration varies greatly along the human gastrointestinal tract, reported as \( \sim 15 \text{mM} \) in ileum (Cummings et al., 1987) compared to between 70 and 140 mM in the proximal colon (Topping and Clifton, 2001). These differences are due to variable microbial SCFA production rates that occur along the human gastrointestinal tract. The variable levels of SCFAs lead to the ascending colon being significantly more acidic than the ileum, with a pH of 5.7 compared to 6.3 (Cummings et al., 1987). It has previously been reported that MCT1 is expressed more highly in human colon than ileum (Englund et al., 2006). Our initial data confirmed that both MCT1 and glycosylated CD147 proteins were predominantly found in membrane-enriched samples (Figures 1C and 1D). We then further confirmed that the proton-dependent MCT1 transporter is more abundant in the human colon membrane-enriched samples compared to ileum membrane-enriched samples (Figure 2), presumably in order to facilitate SCFA transport across colonic cell membranes. This pattern of MCT1 abundance had previously been reported in both humans (Iwanaga et al., 2006) and other mammalian species—including sheep (Kirat et al., 2006a), cows (Kirat and Kato, 2006), goats (Kirat et al., 2006b), and pigs (Welter and Claus, 2008). However, this study is the first to conclusively show a significant reduction in MCT1 abundance in the human sigmoid colon compared to the other colonic regions (Figures 5 and 6). This presumably reflects the varying levels of SCFA production from the different microbial populations along the intestinal tract. For example, SCFA production was found to be eightfold higher from cecal contents than from sigmoid colon contents (MacFarlane et al., 1992). These data are also similar to our previous findings for differential protein abundance of colonic UT-B transporters (Collins et al., 2010), which are also believed to play an important role in the human–bacterial symbiotic relationship that exists in the human colon. Butyrate regulates normal physiology and immune function, along with acetate which is also a naturally occurring mediator of metabolism (MacFarlane and MacFarlane, 2011). As a result, manipulation of gut bacteria, including SCFA-producers, offer targets for health benefit (Marchesi et al., 2016).

As previously described, there still remains controversy concerning the cellular localization of human colonic MCT1 transporters. Many studies have previously reported MCT1 protein to be located on the apical membrane of human colonic cells (Ritzhaupt et al., 1998; Gill et al., 2005; Borthakur et al., 2012). In contrast, but in agreement with another previous human study (Iwanaga et al., 2006), the immunolocalization studies performed with two different antibodies in this study both showed a mainly basolateral location for MCT1 in colonic surface epithelial cells (Figure 3). This was further shown by the colonic MCT1 immunofluorescent staining (Figure 4) in which, despite some cytoplasmic staining being present, the predominant MCT1 signal was clearly in the basolateral membrane region. Our findings strongly suggest that for the tissue samples investigated in this current study, the role of MCT1 was in the transcellular transport of SCFAs across epithelial cells and eventually into the bloodstream, not in apical uptake into the colonocytes.

Potential explanations for the apparent discrepancy in reports of MCT1 human colonic localization include the use of different techniques, alternative cell lines, and varying tissue preparation protocols. For example, studies reporting apical MCT1 have predominantly involved analysis of purified membrane vesicles (Gill et al., 2005) or cell lines, such as C2BBe1 (Borthakur et al., 2012), as opposed to the paraffin-embedded tissues sections utilized in this present study. However, alternative localization of colonic MCT1 has still been reported using the same technique. Most recently, two separate immunolocalization studies contrastingly reported equine MCT1 to be localized apically (Nedjadi et al., 2014) versus basolaterally (Mykkänen et al., 2015) in colonic epithelial cells.

Instead, a more likely explanation could arise from a report that showed how MCT1 has variable cellular localization in different epithelia, with its polarity being dictated by its chaperone CD147 (Castorino et al., 2011). This study hypothesized that the extent of CD147 glycosylation played a key role in determining whether MCT1 was trafficked towards the apical or basolateral membrane in an epithelial cell. Indeed, it has recently been reported that CD147 can also regulate the expression of MCT1 (Walters et al., 2013). Crucially, a previous study in rat cecum and colon showed that the cellular localization of MCT1 co-localized with CD147 could be altered by dietary intake (Kirat et al., 2009). The location of MCT1 changed from basolateral in animals fed control diet, to both basolateral and apical in animals fed pectin-supplemented diets (Kirat et al., 2009). Future studies of MCT1 localization and regulation in the human gastrointestinal tract should therefore include precise investigation of both the extent of CD147 glycosylation and the potential dietary effects.

What is the significance of our findings that MCT1 abundance varies throughout the human colon? With regard to pathology, it has previously been suggested that deficiency in butyrate oxidation in intestinal inflammation is due to reduced MCT1-mediated butyrate uptake (Thibault et al., 2007), with important implications in inflammatory bowel disease (IBD). There may be a homeostatic role in maintenance of body weight or prevention of obesity (Halestrap, 2013; Hermes et al., 2015). Recent studies suggest that MCT1 may play an important role in body weight regulation (Carneiro and Pellerin, 2015). In particular, knockin MCT1 mouse studies have provided strong evidence that during high sugar, high fat dietary intake
intestinal nutrient absorption is significantly reduced in MCT1+/− compared to MCT1+/+ animals (Lengacher et al., 2013). Future studies investigating the potential role of human MCT1 in either IBD or obesity should therefore take great care regarding the location of the colonic samples being utilized. However, perhaps the most important implication is in studies of the role of MCT1 in cancer and its progression.

MCT1 also transports lactate (Cuff et al., 2002) and is believed to play a significant role in the large-scale lactate export that occurs from cancer cells utilizing glycolysis metabolism. Recent studies have shown that blocking MCT1 expression in fibroblasts caused decreases in lactate export, glycolysis, and, hence, tumor growth (Le Floch et al., 2011). Furthermore, while silencing MCT1 or CD147 gives decrease in tumor growth, silencing of CD147 with the maintenance of MCT1 had no effect. This represents strong evidence that MCT1 could be a key target for cancer therapy (Le Floch et al., 2011). More recently, co-expression of MCT1 and CD147 has been associated with low survival in patients with gastrointestinal stromal tumors (de Oliveira et al., 2012). Indeed, it has now been demonstrated that MCT1-mediated transport can be used to effectively deliver toxic substances to glycolytic tumors (Birsoy et al., 2013). Most promisingly, the latest studies have shown that disruption of MCT1 and CD147 can indeed sensitize glycolytic tumors to anticancer treatment (Marchiq et al., 2015). It is therefore apparent that precise, detailed understanding of the normal physiological regulation of colonic MCT1 transporters may facilitate improvements in both cancer treatment and patient survival.

Finally, the differential abundance of transporters within the human colon may be viewed as particularly important in view of recent findings concerning cancer development. For example, a recent study has shown that microbial biofilms may potentially be much more prevalent in proximal compared to distal colorectal cancers (Dejea et al., 2014). Another study has suggested that colonic cancer can be classified into four distinct molecular subtypes (Guinney et al., 2015). Future research should therefore further investigate the potential links between abundance of epithelial transporters (e.g., MCT1) with colonic region, microbial environmental factors, and molecular subtypes, rather than simply regarding all colonic cancers as one disease.

In conclusion, this study has shown that MCT1 transporter protein is predominantly found in the basolateral membrane of surface epithelial cells within the ascending, transverse, and descending colon. These findings have important implications for any future studies investigating the potential role of MCT1 transporters within human colonic health and disease.

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