The peptide transporter PEPT1 is expressed in distal colon in rodents and humans and contributes to water absorption

Tilo Wuensch,1 Stephan Schulz,2,3 Sina Ullrich,1 Nicole Lill,1 Tamara Stelzl,1 Isabel Rubio-Aliaga,1 Gunnar Loh,3 Mathias Chamaillard,5 Dirk Haller,6 and Hannelore Daniel1
1Technische Universität München, Biochemistry Unit, ZIEL-Research Center for Nutrition and Food Science, CDD-Center for Diet and Disease, Freising-Weihenstephan, Germany; 2Technische Universität München, Klinikum rechts der Isar, Institute of Pathology, Munich, Germany; 3Institute of Pathology, Charité-Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany; 4German Institute of Human Nutrition, Department of Gastrointestinal Microbiology, Nutnthal, Germany; 5Institut Pasteur de Lille, Center for Infection and Immunity of Lille, Lille, France; and 6Technische Universität München, Biofunctionality Unit, ZIEL-Research Center for Nutrition and Food Science, CDD-Center for Diet and Disease, Freising-Weihenstephan, Germany

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Wuensch T, Schulz S, Ullrich S, Lill N, Stelzl T, Rubio-Aliaga I, Loh G, Chamaillard M, Haller D, Daniel H. The peptide transporter PEPT1 is expressed in distal colon in rodents and humans and contributes to water absorption. Am J Physiol Gastrointest Liver Physiol 305: G66–G73, 2013. First published May 9, 2013; doi:10.1152/ajpgi.00491.2012.—The peptide transporter PEPT1, expressed in the brush border membrane of enterocytes, mediates the uptake of di- and tripeptides from luminal protein digestion in the small intestine. PEPT1 was proposed not to be expressed in normal colonic mucosa but may become detectable in inflammatory states such as Crohn’s disease or ulcerative colitis. We reassessed colonic expression of PEPT1 by performing a systematic analysis of PEPT1 mRNA and protein levels in healthy colonic tissues in mice, rats, and humans. Immunofluorescence analysis of different mouse strains (C57BL/6N, 129Sv, BALB/c) demonstrated the presence of PEPT1 in the distal part of the colon but not in proximal colon. Rat and human intestines display a similar distribution of PEPT1 as found in mice. However, localization in human sigmoid colon revealed immunoreactivity present at low levels in apical membranes but substantial staining in distinct intracellular compartments. Functional activity of PEPT1 in colonic tissues from mice was assessed in everted sac preparations using [14C]Gly-Sar and found to be 5.7-fold higher in distal colon compared with proximal colon. In intestinal tissue from Pept1−/− mice, no [14C]Gly-Sar transport was detectable but feces samples revealed significantly higher water content than in wild-type mice, suggesting that PEPT1 contributes to colonic water absorption. In conclusion, our studies unequivocally demonstrate the presence of PEPT1 protein in healthy distal colonic epithelium in mice, rats, and humans and proved that the protein is functional and contributes to electrolyte and water handling in mice.
preparations of small intestine and colon obtained from wild-type and Pept1-deficient (Pept1−/−) mice with glycy-l-sarcosine (Gly-Sar) as a specific Pept1 substrate.

MATERIALS AND METHODS

Ethics statement. Animal-use protocols were approved by the Bavarian Animal Care and Use Committee (AZ 55.2-1-54-2531-164-09). Samples from patients were collected in accordance with the Declaration of Helsinki.

Animals. Three wild-type mouse strains of different genetic backgrounds (C57BL/6N, 129/Sv, BALB/c) were used. Furthermore, tissues of transgenic (Pept1−/−) mice lacking Pept1 (14) as well as intestinal samples from Wistar rats and germ-free mice [German Institute of Human Nutrition (DIfE), Potsdam, Germany] were used. Germ-free mice (C3H/HeOuJ) kept at the German Institute of Human Nutrition (DIfE) were housed in Trexler-type isolators in polycarbonate cages on g-irradiated wood chips. Room temperature was maintained at 22 ± 2°C and air humidity at 55 ± 5%. The animals had free access to sterilized feed (Altromin fortified type 1310, Altromin, Lage, Germany) and autoclaved drinking water.

Transport studies. Pept1-mediated transport was measured in vitro in everted sacs prepared from jejunal as well as proximal and distal colon of wild-type and Pept1−/− mice. Individual 4- to 5-cm-long intestinal segments were rinsed immediately after removal with saline (0.9% NaCl solution) and everted with a metal rod. One end was ligated with star thread and the sac was filled with Krebs bicarbonate buffer (KBB, 119 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 1.2 mM MgSO4, 1.2 mM KH2PO4, 25 mM NaHCO3, pH 7.4) and closed. Tissues were incubated for 15 min in 5 ml substrate-containing incubation buffer [119 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl2, 1.2 mM MgSO4, 1.2 mM KH2PO4, 25 mM NaHCO3, 1.01 mM 2-(N-morpholino)ethanesulfonic acid, pH 6.0] continuously gassed with carbogen at 37°C on a shaking platform. Radio-labeled [14C]Gly-Sar (GE Healthcare, Munich, Germany) with a specific activity of 0.5 Ci/mmol was used as a specific Pept1 substrate. After incubation, the sacs were washed three times in KBB before the serosal fluid was collected and the tissue dried at 55°C. Samples were homogenized in 400 μl of Tris, pH 7.4) for 30 min, washed, and incubated with primary antibodies against PEPT1 (1:1,000; C-19, Santa Cruz Biotechnology, Santa Cruz, CA), goat polyclonal antibody against villin (1:1,000; C-19, Santa Cruz Biotechnology) for 3 h slightly shaking at room temperature. The membrane were washed three times and incubated with appropriate IRDye-labeled secondary antibodies (1:10,000; LI-COR Biosciences, Bad Homburg, Germany) for 1.5 h. Proteins were visualized using an infrared scanner (Odyssey, LI-COR Biosciences). Band intensities were quantified by use of the Odyssey Application Software (V3.0) provided with the imager station. Pept1 expression was normalized to the expression of the reference proteins villin and β-actin.

Quantitative real-time RT-PCR. RNA was isolated from mucosal scrapings by use of the TRIzol reagent (Invitrogen, Darmstadt, Germany). The final RNA pellet was dissolved in RNase-free water (Qiagen, Hilden, Germany), and RNA yields and integrity were confirmed spectroscopically by using a Nanodrop ND-1000 (PEQLAB Biotechnologie, Erlangen, Germany) device and by gel electrophoresis before use. First-strand cDNA was synthesized from 2.5 μg isolated RNA using the ReverTaid Premium First Strand cDNA synthesis kit (Fermentas, St. Leon-Rot, Germany) following the manufacturer’s protocol. The cDNA was stored in nuclease-free water (Qiagen) at −20°C until use. RT-PCR reactions were performed in duplicate by using the Maxima SYBR Green/ROX qPCR Master Mix. Primer sequences are listed in Table 1. Cycling conditions were as follows: initial denaturation for 8 min at 95°C, followed by 35 cycles denaturation for 95°C for 15 s, annealing for 30 s at 60°C, and elongation for 30 s at 72°C. Melting curve analysis was carried out from 60 to 95°C with a temperature transition rate of 0.1°C/s.

The expression of Pept1 was normalized to the housekeeping genes Villin, β-Actin, and Gapdh and expressed as fold difference to the expression in wild-type jejunum, by use of the 2−ΔΔCt calculation (9). Amplified PCR products were qualitatively analyzed by electrophoresis through a 1% agarose gel and stained with ethidium bromide to

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Table 1. Primer sequences used for quantitative RT-PCR (5’-3’)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Accession No.</th>
<th>Forward Primer Sequence</th>
<th>Reverse Primer Sequence</th>
<th>Product size, bp</th>
<th>Temperature (forward, reverse), °C</th>
</tr>
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<tbody>
<tr>
<td>Pept1</td>
<td>NM_053079.2</td>
<td>ACC CTT TGA GCA TCT TCT TC</td>
<td>GCG ATG AGA GCT CCA AGA AT</td>
<td>187</td>
<td>59.3, 59.5</td>
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<tr>
<td>β-Actin</td>
<td>NM_007393</td>
<td>GAA ATG CTT GGT GGT AAC ATG AA</td>
<td>AAG GAA GCC TGG AAA AGA GC</td>
<td>179</td>
<td>60.7, 60.0</td>
</tr>
<tr>
<td>Villin</td>
<td>NM_009509.2</td>
<td>CTG TCG GAC GGA GAA AAG AG</td>
<td>GAA CAC ATC CTC CTC CTC CA</td>
<td>220</td>
<td>60.0, 60.0</td>
</tr>
<tr>
<td>Gapdh</td>
<td>NM_008084.2</td>
<td>ACT CCA CTC ACG GCA AAT TC</td>
<td>TCT CCA TCG TGG TGA AGA CA</td>
<td>171</td>
<td>60.1, 60.1</td>
</tr>
</tbody>
</table>

determine the predicted product length (Pept1, 187 bp; Villin, 220 bp; β-Actin, 179 bp; Gapdh, 171 bp) (Fig. 2A).

Fecal water content. Fresh fecal samples were collected from wild-type and Pept1−/− mice (n = 7), 1 h after the onset of the light phase. Mice were allowed to regular drink and eat ad libitum prior to feces collection. To obtain fresh fecal samples, single mice were placed in an empty cage for 1 min; the secreted feces were weighed and dehydrated in a drying oven (BINDER, Tuttlingen, Germany) at 50°C overnight. Fecal water content (%) was calculated as follows: [(fecal wet wt – fecal dry wt)/fecal wet wt] × 100.

Human samples and subject characteristics. All analyzed human tissue samples were archived paraffin-embedded material of specimens from patients, generated for routine diagnostics. Each of the patients had signed a written agreement for the usage of residual tissue specimens for scientific purpose, according to the guidelines of the Charité-University Medicine Berlin. The samples were evaluated by tissue histology as free from necrotic, cancerous, or inflammatory lesions. All human tissue samples were obtained from male donors with a mean age of 44 ± 16.74 yr. In total three tissue samples of small intestine and five samples of colon ascendens and colon sigmoides, respectively, were analyzed.

Statistical analysis. The results are expressed as means ± SE. Statistical analysis were performed with GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Statistically significant differences were defined as *P < 0.05, **P < 0.01, and ***P < 0.001.

RESULTS

PEPT1 expression in healthy murine colon. PEPT1 was detectable with high density in brush border membranes along the small intestine from duodenum to ileum of C57BL/6N wild-type mice. In colon, PEPT1 showed a distinct pattern of distribution with marked differences between proximal and distal segments. No staining was obtained in proximal colon, while significant immunoactivity was found from mid colon to rectum. Identical PEPT1 expression patterns were observed in two other wild-type mouse strains (Balb/c and 129/Sv) of different genetic background (Fig. 1A). No PEPT1 signal was detectable in intestinal tissue of Pept1−/− mice (Fig. 1B).

Immunofluorescence-based findings were confirmed by Western blot analysis in C57BL/6N wild-type mice (Fig. 1C). The PEPT1 band showed highest densities in duodenum, jejunum, and ileum, whereas it was essentially absent in proximal colon but became detectable again in samples of distal colon. No PEPT1 band was detectable in any intestinal tissue sample of Pept1−/− mice. Densitometric quantification with normalization of PEPT1 abundance to the reference proteins Villin or β-actin revealed in distal colon a PEPT1 density accounting to 40% of that found in small intestine. Expression levels in proximal colon were ~3.6-fold lower (P < 0.05) than in distal colon (Fig. 1D). When intestinal tissues of three 12-wk-old germ-free mice were evaluated, all showed consistently a similar PEPT1 expression pattern compared with their conventionally housed littermates, suggesting that the microbiota does not influence colonic PEPT1 expression (Fig. 1E).

PEPT1 is highly glycosylated and we detected PEPT1 with an apparent mass of 95 kDa in the small intestine but with ~110 kDa in colonic samples. Treatment of the protein lysates with PNGase F resulted in a decrease of the molecular weight from small intestinal and colonic PEPT1 toward ~71 kDa (Fig. 1F), corresponding to the proposed molecular weight of the native nonglycosylated PEPT1 protein (2).

Pept1 mRNA copy numbers were determined by quantitative real-time RT-PCR with specific primers mapping a 187 bp sequence intron spanning of the 3rd and 4th exon within the Pept1 gene. Data were normalized to the three housekeeping genes Villin, β-Actin, and Gapdh and colonic expression levels are displayed relative to that of jejunum. Intestinal tissues from Pept1−/− mice lacked the mRNA (Fig. 2A). In wild-type mice Pept1 mRNA levels declined from duodenum to ileum. In colon, substantial Pept1 mRNA was detectable in distal regions with 5.2-fold higher (P < 0.001) levels compared with those of proximal colon, pointing to the differential regulation of Pept1 expression at the mRNA level (Fig. 2B).

Functional analysis of PEPT1 in colonic tissues. By using [14C]Gly-Sar as substrate, highest uptake rates were observed in jejunum (19.76 nmol·20 min·1·mg protein−1) followed by distal colon (1.71 ± 0.42 nmol·20 min·1·mg protein−1) and significant lower uptake rates in proximal colon (0.30 ± 0.22 nmol·20 min·1·mg protein−1) of wild-type mice. Addition of 50 mM unlabeled Gly-Sar competitively reduced the uptake in small intestine by 88.4 and by 70.7% in distal colon. [14C]Gly-Sar influx into tissues of Pept1−/− mice was very low and could not be inhibited and thus may be attributed to passive diffusion (Fig. 3A). These results demonstrate that PEPT1 is functional in the colon.

Since PEPT1 was previously shown to contribute to intestinal fluid absorption (6), we determined fecal water content as a surrogate for PEPT1 activity in the intestine; this revealed significantly elevated water content in feces of Pept1−/− (67.9 ± 3.0 vs. 55.5 ± 3.4%; P < 0.001) compared with wild-type mice (Fig. 3B). PEPT1-mediated transport of di- and tripeptides contributes to net water absorption under normal physiological conditions.

PEPT1 distribution in rat and human tissues. The distinct, spatial colonic PEPT1 expression is not restricted to mice. Immunostainings in rat and human intestine revealed similar expression profiles as found in mice. The absence of PEPT1 in proximal and its presence in distal colonic epithelium was comparable between the species. In contrast to mice, however, PEPT1 in distal colonic tissue from rats revealed a reduced apical membrane staining but could not be inhibited and thus may be attributed to passive diffusion (Fig. 3A). These results demonstrate that PEPT1 is functional in the colon.

Instead of PEPT1, we previously shown to contribute to intestinal fluid absorption (6), we determined fecal water content as a surrogate for PEPT1 activity in the intestine; this revealed significantly elevated water content in feces of Pept1−/− (67.9 ± 3.0 vs. 55.5 ± 3.4%; P < 0.001) compared with wild-type mice (Fig. 3B). PEPT1-mediated transport of di- and tripeptides contributes to net water absorption under normal physiological conditions.

Pept1 distribution in rat and human tissues. The distinct, spatial colonic PEPT1 expression is not restricted to mice. Immunostainings in rat and human intestine revealed similar expression profiles as found in mice. The absence of PEPT1 in proximal and its presence in distal colonic epithelium was comparable between the species. In contrast to mice, however, PEPT1 in distal colonic tissue from rats revealed a reduced apical membrane staining but increased labeling of intracellular compartments (Fig. 4). A comparable distribution with intracellular localization was found in human intestines (Fig. 5). Costaining with GM130, a member of the golgin family of coiled-coil proteins, expressed on the cis-face of the Golgi compartment (21), revealed, beside scattered apical membrane staining, colocalization of PEPT1 with GM130 in distal colon (Fig. 5, B and C). This suggests that in rats and
PEPT1 IS EXPRESSED IN HEALTHY COLON

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Fig. 1. PEPT1 expression in mouse small intestine and colon. A: representative image of a mouse colon, including cecum and terminal ileum (arrow) (top). Black bars on the colon illustrate the defined sampling regions from proximal to distal of which immunofluorescence stainings (bottom) have been performed on tissues from C57BL/6, BALB/c, and 129/Sv mice \( (n = 1–7) \). PEPT1 (red) is expressed on the apical membrane of the small intestinal epithelium, not detectable in proximal colon but, notably, its immunoreactivity increased from mid colon toward the rectum. DRAQ5 was used as nuclear counterstain. B: no PEPT1 immunoreactivity was in small intestinal or colonic samples of Pept1 \(^{-/-}\) mice. C: representative Western blot analysis of a wild-type (left) and a Pept1 \(^{-/-}\) (right) mouse intestine. The specific PEPT1 band appeared at \( \sim 95 \) kDa and was detectable in duodenum (Duo), jejunum (Jej), and ileum (Ile). PEPT1 was not detectable in proximal colon (Col p) but was in distal colon (Col d) from wild-type mice. Noteworthy, PEPT1 appears with a \( \sim 10 \) kDa higher molecular weight in distal colon compared with small intestine. Villin and \( \beta\)-actin were used as loading controls and for quantification. D: densitometric quantification showed the highest PEPT1 expression in jejunum and substantial expression in distal colon, significantly higher compared with proximal colon. Villin (left) and \( \beta\)-actin (right) were used as reference proteins \((n = 5–8, *P < 0.05)\). E: immunofluorescence staining of PEPT1 (red) in small intestine and colon samples obtained from germ-free mice. DRAQ5 was used as nuclear counterstain. F: deglycosylation of PEPT1 from wild-type mouse jejunum and distal colon with PNGase F (+) resulted in a molecular mass shift from \( \sim 95 \) kDa (jejenum) or \( \sim 105 \) kDa (distal colon) to a band at \( \sim 71 \) kDa corresponding to the proposed molecular mass of the nonglycosylated PEPT1 protein.

DISCUSSION

The objective of the present study was to systematically determine the expression profile of the peptide transporter PEPT1 in healthy rodent and human small intestine and colon. The anti-PEPT1 antibodies used for immunofluorescence stainings and Western blot analysis detected specifically the PEPT1 protein. In tissues of Pept1 \(^{-/-}\) mice no immune reactivity was observed and incubation with preimmune serum as well revealed no labeling. Pept1 transcript levels showed comparable

humans the PEPT1 protein also resides in the cis-Golgi as part of the trafficking route to the apical membrane.
tissue and side-specific expression patterns in identical samples as used for immunofluorescence or Western blotting.

Our data confirm that PEPT1 is most abundantly expressed in small intestine with highest expression in duodenum, lower levels toward the ileum and highest transport in jejunum (11, 15). However, PEPT1 expression was also found in healthy colon from mice, rats, and humans in distal but not proximal segments. That PEPT1 is functional in distal colon was demonstrated by tracer flux studies with $^{[14C]}$Gly-Sar and specificity was shown by using $\text{Pept}1^{-/-}$ mice as a control. Moreover, functional analysis demonstrated in essence that transport function follows protein abundance with a distinct segment-specific pattern. These findings are consistent across various species with expression and functionality of PEPT1 in distal but not proximal colon of healthy animals and humans.

To date, controversial findings about colonic PEPT1 expression exist. Although several studies failed to detect PEPT1 expression in colon (10, 11, 15, 22) some other reports suggested the presence of PEPT1 in healthy colon from mice, rabbits, and humans (12, 13, 15, 19, 37). Regional differences between proximal and distal colon have also been mentioned but not systematically investigated. Jappar et al. (15) reported higher $\text{Pept}1$ levels in distal compared with proximal colon in mice but could not detect PEPT1 protein in colon. The region-specific colonic $\text{Pept}1$ expression was also found in 8-wk-old Dutch rabbits by in situ hybridization by Freeman et al. (13), who detected a weak $\text{Pept}1$ signal in proximal colon but could not distinguish $\text{Pept}1$ expression in distal colon from the background signal. In humans, the studies by Meier et al. (19) offered evidence for a region-specific expression as well and...
the work by Ford et al. (12) described the predominantly basal and basolateral localization of PEPT1 in colonicocytes toward the base of the crypt but apical localization toward the luminal surface. In the present study a distinct proximal to distal distribution pattern of PEPT1 was observed by immunofluorescence and Western blot analysis in mice, rats, and humans with discrete differences at the subcellular level between mice and rats and humans. Although the three mouse strains studied revealed solely brush border membrane staining in distal colon, pronounced differences appeared in surface expression and intracellular localization in samples from rat and human distal colon. There, PEPT1 was detectable in scattered apical staining but with prominent intracellular cis-Golgi associated immunoreactivity. These species-dependent differences in PEPT1 trafficking and localization are intriguing. In *rab8* gene-deficient mice (25) it has been shown that this small GTP-binding protein controls PEPT1 apical membrane localization that also involves protein-protein interactions via PDZK1 (28). Trafficking of PEPT1 within the Golgi and to the plasma membrane could therefore be regulated differently in mice or humans. These data emphasize that the site of tissue sampling is most crucial for interpretation of data on PEPT1 expression because of species and region specific differences in levels and sites of expression in apical surface and subcellular regions.

Although peptides are constantly produced by protein degradation and may also be present in larger quantities in the contents of the large intestine, the importance of PEPT1 in distal colon and rectum in handling of di- and tripeptides remains to be determined. However, the intestinal peptide uptake with subsequent intracellular hydrolysis has been demonstrated to be a driving force for water uptake (1). And the PEPT1-mediated di- and tripeptide absorption has been shown in this context to be accompanied by a substantial concomitant salt and fluid absorption (6). Evidence for this role was also accompanied by a substantial concomitant absorption (6). Evidence for this role was also demonstrated here based on increased water content on feces of *Pept1*−/− mice.

As proposed, peptides presented to PEPT1 in the colon may also include the proteolytic products of peptidoglycans such as MDP, fMLP, and tri-DAP (5, 7, 32). Moreover, the demonstrated effects of these peptides on NOD2 and neutrophil activation suggested that PEPT1 may act as an amplifier of inflammation by delivery of these proinflammatory compounds to tissues and even more so, when transporter expression is increased in IBD (20). Our findings that PEPT1 is expressed in healthy colon, irrespective of the presence or absence of intestinal microbiota, and that *Pept1*−/− mice show normal intestinal morphology and no gross or histological evidence of a phenotypic effect when housed under conventional conditions challenge this concept that PEPT1 may act as an amplifier of inflammation when expressed in colon.

A recent targeted PEPT1 gene polymorphisms analysis in two Scandinavian cohorts revealed that *Pept1* gene polymorphisms may associate with IBD susceptibility (38). Most surprisingly, a Ser117Asn exchange in the protein coding region appeared to be protective against Crohn’s disease in the cohort from Finland, whereas the same polymorphism in the Swedish cohort was associated with an increased susceptibility to Crohn’s disease. These controversial findings demonstrate the need to better define the presence or absence of PEPT1 expression and its function, taking into account its discrete spatial expression pattern in colon. It needs to be emphasized that increased PEPT1 protein expression levels in IBD samples have only been reported once by immunohistochemistry-based staining for human PEPT1 in one ulcerative colitis and one Crohn’s disease sample without specification of the origin of the samples (20).

We demonstrate here that the region of tissue sampling is crucial for detection of PEPT1 mRNA or protein in colon because of region- and species-specific differences in levels and sites of expression.

Although it cannot a priori be excluded that differences in the microbiota may contribute to those species differences, germ-free mice revealed the same localization pattern as conventionally housed mice, suggesting that species rather than the gut microbiota defines the differences. However, further studies are needed to determine whether the protein abundance is also similar in germ-free and conventionally housed mice. Regarding PEPT1 localization, rats rather than mice are closer to humans and may be more useful in assessing colonic functions of PEPT1 and its role in IBD.

Taken together, the seemingly controversial findings on the presence of PEPT1 in normal mammalian colon and its specific

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**Fig. 4. PEPT1 expression in rat small intestine and colon.** PEPT1 is expressed in the apical membrane of jejunum in rats. PEPT1 expression is not detectable in proximal colon but is in distal colon. In distal colon, the PEPT1 signal appears predominantly intracellular rather than in the apical membrane. MCT-1 (green) was used as marker of basolateral membranes to visualize the distribution and borders of enterocytes. DAPI was used as nuclear counterstain (blue).
role in IBD require a reassessment in view of its discrete spatial expression pattern in healthy distal but not proximal colon in mice, rats, and humans. The regional differences in PEPT1 expression in distal vs. proximal colon indicate that this must be taken into account in future studies to address its role in healthy colon and IBD. In mice our evidence suggests that PEPT1 contributes to water absorption but its absence in Pept1−/− mice does not result in any gross or histological phenotypic impairment of small intestine or colon. Further studies will be required to establish the impact of intestinal inflammation on PEPT1 expression and its functional role during IBD.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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