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# The Expression of Cytokeratins in Bovine Intestinal Microfold (M) Cells

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## 1. Introduction

The mucosal surface of the gut is exposed to a variety of foreign antigens and microorganisms, some of which are potentially harmful for the host. To protect against the risk of infection, the intestinal mucosa has developed specialized organized lymphoid tissues and epithelial cells. The gut-associated lymphoid tissues (GALT) including Peyer's patches (PPs) are major inductive sites for intestinal immunity. Different from other peripheral lymphoid tissues, GALT lacks afferent lymphatics, and directly samples mucosal antigens across the epithelial barrier to initiate antigen-specific immune responses. This task is accomplished by specialized epithelial cells within the follicle-associated epithelium (FAE) covering the lymphoid follicles of GALT known as microfold (M) cells.

M cells possess a high capacity for phagocytosis and transcytosis, and these functions allow the rapid transport of antigens into the underlying lymphoid tissues, especially antigen-presenting cells. Antigens are then presented to T cells that support B-cell activation, resulting ultimately in the generation of IgA-producing plasma cells. Thus, M-cell-mediated antigen transport is important for the initiation of mucosal immune responses (Kraehenbuhl and Neutra, 2000; Neutra et al., 1996; Neutra et al., 2001). In order to express their specialized functions including phagocytosis and transcytosis, M cells exhibit unique morphologies that differ from the surrounding absorptive enterocytes. M cells lack a dense microvilli brush border structure, though they do possess shorter and irregular microvilli on their apical surface. On the basolateral side, a pocket-like invagination of the plasma membrane is formed to house lymphocytes and antigen-presenting cells (Neutra et al., 1996).

These morphological features of M cells have an effect on the composition of the cytoskeletal proteins within the cell, such as actin-containing microfilaments, intermediate filaments and their associated proteins. For example, the lack of a brush border in M cells is reflected in the cellular localization of the actin and villin, resulting in unusual staining patterns of these proteins in M cells of mice and calves, as actin and villin are essential proteins for microvilli formation (Kanaya et al., 2007; Kerneis et al., 1996). In addition to the abnormal cellular localization of actin and actin-related proteins, some investigators have demonstrated that intermediate filament proteins such as vimentin and cytokeratins can be used as

immunohistochemical markers for M cells. Gebert *et al.* have shown that CK18 is a sensitive marker for porcine M cells (Gebert *et al.*, 1994) while vimentin is selectively expressed in rabbit M cells (Jepson *et al.*, 1992). M cells in rats are detected by monoclonal antibodies raised against CK8 (Rautenberg *et al.*, 1996). These preferential expressions of intermediate filaments in M cells indicate the substantial roles of CKs and vimentin in M cell morphology and function.

In this chapter, we introduce a number of experiments that we have done with respect to the expression of CK18 in bovine M cells. And we further discuss the relationship between the expressions of CKs and the development and apoptosis of bovine intestinal M cells.

## 2. Material and methods

In this study, we performed several histological and electron microscopical analyses. The monoclonal antibodies for immunohistochemistry are summarized in Table 1. The detailed procedures have been described in our previous reports (Hondo *et al.*, 2011; Miyazawa *et al.*, 2006).

## 3. Results

### 3.1 Localization of M cells in FAE of jejunum and ileum PPs

The distribution and size of PPs in ruminants, including cattle, have several unusual features. PPs in the jejunum resemble those of other mammalian species. In addition to these jejunal PPs, however, ruminants possess another type of PPs in the ileum. These ileal PPs make up about 15% of the length of the small intestine, and are thought to be mature before birth and involute at a young age, in a similar way to the thymus gland (Beyaz and Asti, 2004; Landsverk, 1979, 1984; Reynolds and Morris, 1983). In order to observe the localization of bovine M cells in both jejunal and ileal PPs, we examined the ultrastructure of the FAE by scanning electron microscopy (SEM) in 13 weeks old calves. In jejunal PPs, M cells were randomly distributed in the FAE as for other species (Figure 1). On the other hand, the FAE of ileal PPs were almost filled with M cells having irregular microvilli (Figure 1). These observations are consistent with previous reports (Kanaya *et al.*, 2007; Landsverk, 1984).

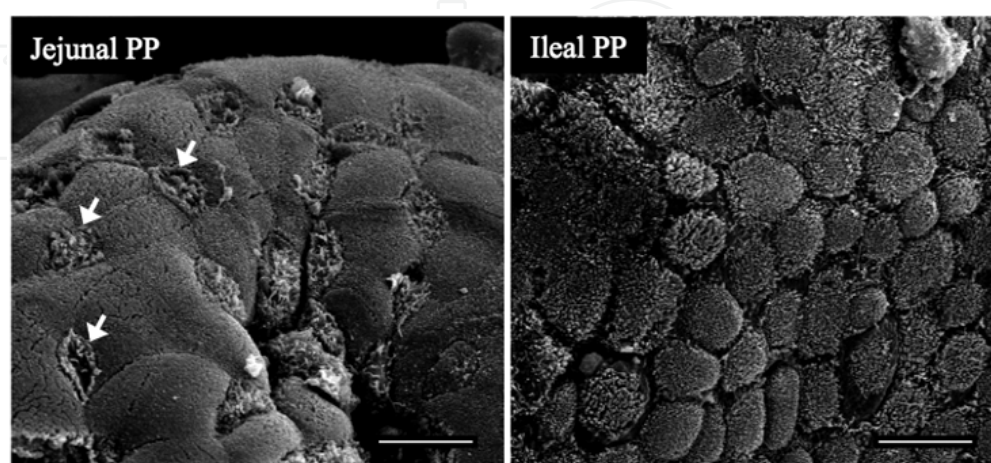


Fig. 1. Scanning electron microscopy (SEM) of follicle-associated epithelium (FAE) in bovine Peyer's patches (PPs).

The specimens of PPs were fixed with 2.5% glutaraldehyde and coated with platinum-palladium for SEM analysis. SEM shows the distribution of M cells in the FAE of jejunal PPs and ileal PPs. Arrows show M cells possessing irregular and sparse microvilli in jejunal PPs. The FAE of ileal PPs is filled with M cells. Bars = 10  $\mu$ m.

3.2 Expression of CK18 in bovine M cells

As described above, some intermediate filament proteins, such as CK8, CK18, and vimentin, are known to be marker for M cells in the intestine. Therefore, we investigated the expressions of these proteins in bovine PPs (see table 1). As a result of this, we identified that several monoclonal antibody clones for CK18 were preferentially stained in the FAE and crypts of both jejunal and ileal PPs (Figure 2, 3A and B). CK20 was detected strongly in both the villous epithelium and FAE, but not in the crypts. In contrast, CK7, CK8 and CK19 could not be detected in the whole of the small intestinal epithelium, and vimentin was only detected in the stromal cells of subepithelial tissues (Figure 2 and Table 1). The positive CK18 signal in the FAE of jejunal and ileal PPs was similar to the distribution of M cells recognized by SEM. In order to confirm the expression of CK18 in bovine M cells, we investigated the ultrastructure of CK18-positive cells in the FAE. In jejunal FAE, CK18-positive cells had irregular and sparse microvilli and pocket-like structures containing lymphocytes (Figure 3C and E). In the sections of ileal FAE, we clearly observed that CK18-positive cells had broader microfolds on their apical surface, and CK18-negative cells had dense microvilli (Figure 3D and F). In addition to the preferential expression of CK18 in M cells, CK18 was also detected in the crypts (Figure 2). Therefore, we investigated the proliferative activity of CK18-positive cells in the crypt using the mirror section technique. A couple of mirror sections revealed that all Ki-67 positive proliferative cells in the crypt were positive for CK18 (Figure 4). These results suggest that CK18 is a marker for M cells in the both jejunal and ileal FAE, and proliferative cells in the crypts of the bovine small intestine.

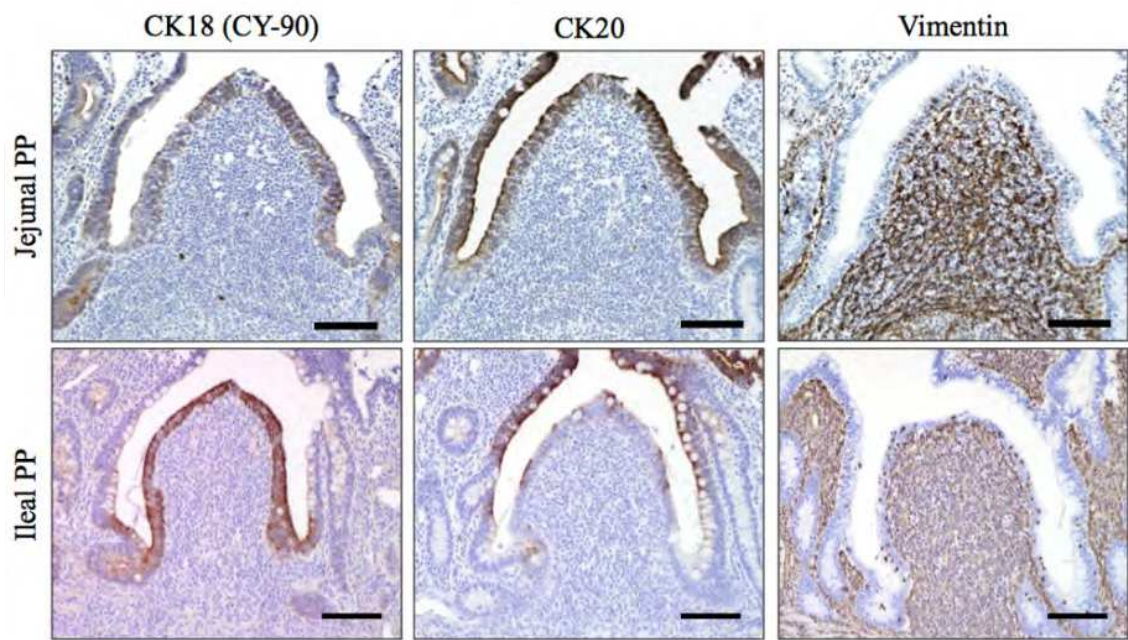


Fig. 2. Expression of cytokeratins and vimentin in bovine PPs.



The sections were immunostained with anti-cytokeratin (CK) 18 (CY-90), anti-CK20 and anti-vimentin monoclonal antibodies. Bars = 100 μm.

Specificity	Isotype	clone#	Dilution	Staining patterns
Pan-CK	Mouse IgG <sub>1</sub>	C-11	1: 2000	M cells, crypt
CK7	Mouse IgG <sub>1</sub>	RCK105	1: 1000	N. D.
CK8	Mouse IgM	35βH11	Ready to use	N. D.
CK18	Mouse IgG <sub>1</sub>	CY-90	1: 1000	M cells, crypt
CK18	Mouse IgG <sub>1</sub>	Ks-B17.2	1: 1000	M cells, crypt
CK18	Mouse IgG <sub>1</sub>	CK5	1: 500	M cells, crypt
CK19	Mouse IgG <sub>2a</sub>	A53-B/A2	1: 100	N. D.
CK20	Mouse IgG <sub>2a</sub>	Ks20.8	1: 2	Villus epithelium, FAE enterocytes
Vimentin	Mouse IgG <sub>2a</sub>	VIM 3B4	Ready to use	Sub epithelium
Ki67	Mouse IgG <sub>1</sub>	MIB-1	1: 100	Proliferative cells

Table 1. The list of monoclonal antibodies against intermediate filaments proteins.

The specificity, isotypes, clone numbers, dilution for immunostaining and staining patterns in bovine PPs of antibodies against intermediate filament proteins are summarized. N. D. means “Not detectable”.

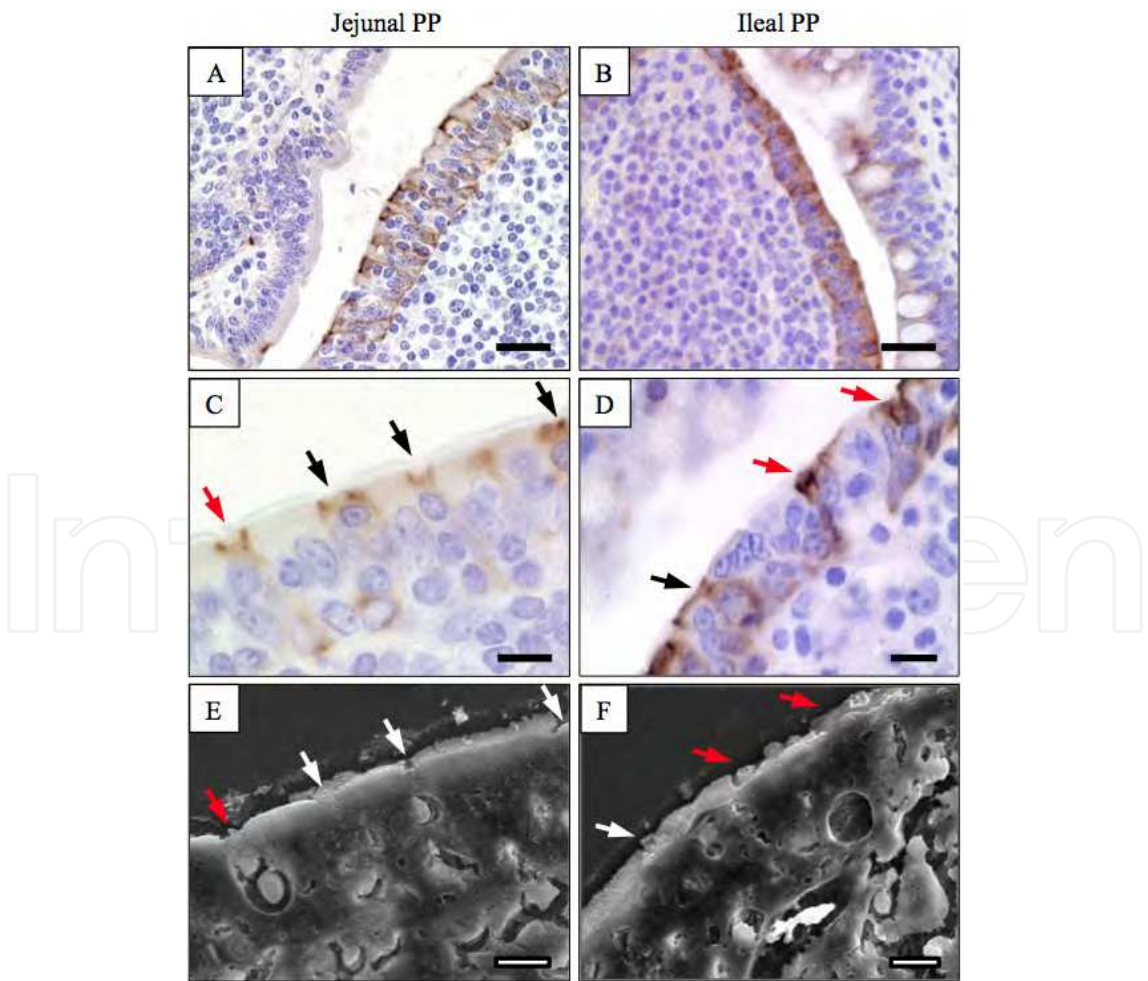


Fig. 3. Ultrastructure of CK18-positive cells in bovine PPs.

CK18-positive cells showed M-cell like distribution in the FAE of jejunal and ileal PPs (A and B). A couple of mirror sections were used for the identification of CK18-positive cells. One section was stained with anti-CK18 (CY-90) monoclonal antibody (C and D). The other was fixed with glutaraldehyde, treated with tannic acid, and coated with platinum-palladium for SEM analysis (E and F), respectively. Arrows show identical cell types. Bars = 30  $\mu$ m (A and B) and 10  $\mu$ m (C-F).

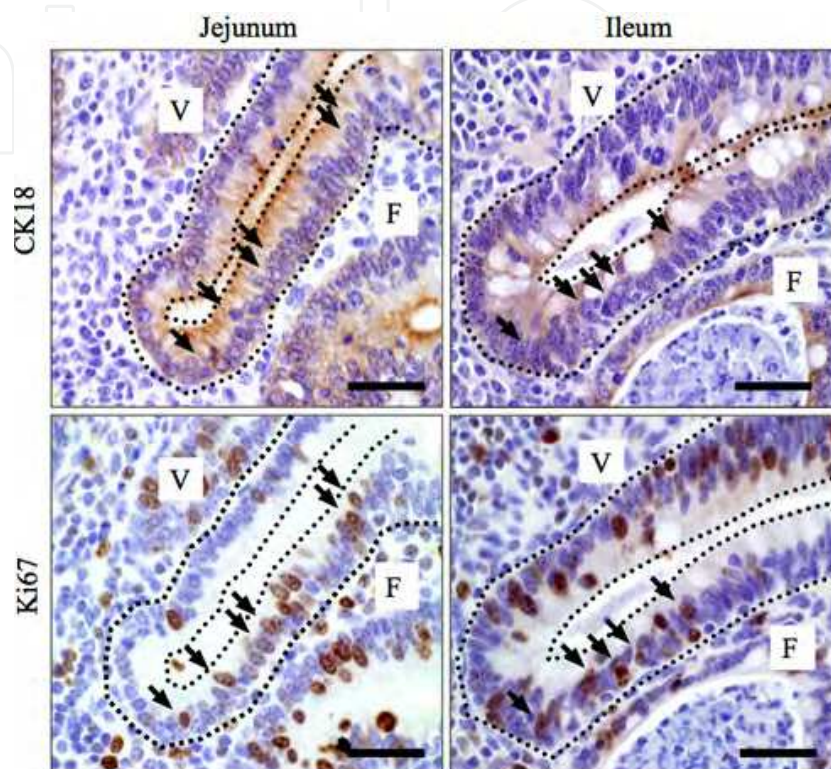


Fig. 4. Localization of CK18-positive cells in the crypts

For the identification of CK18-positive cells in the crypts, we prepared a couple of mirror sections of crypts containing villous epithelium (V) and FAE (F), which were immunostained with anti-CK18 monoclonal antibody or anti-Ki67 monoclonal antibody, a marker of proliferation. Arrows show Ki67-positive cells. Dotted lines show the epithelial cells of the crypts. Bars = 30  $\mu$ m.

### 3.3 The relationship of CK18 and CK20 in the bovine FAE

CK20 was observed not only throughout the epithelial cells lining villous epithelium, but also in the partial cells of the FAE (Figure 2). These results demonstrate that both CK18 and CK20 are co-expressed in the FAE-crypt axis. Therefore, we investigated the expression of these CKs in the FAE-crypt axis by dual staining of CK18 and CK20. As described above, the preferential expression of CK18 was observed in the M cells of the FAE and proliferative cells in the crypts. On the other hand, CK20 positive signals were exclusively observed in the CK18-negative cells including the partial of the FAE cells and the whole of villous epithelial cells (Figure 5A-D). These results indicate that proliferative cells in the crypts exchange CK18 for CK20 once above the mouths of crypts when they have moved to the villi, whereas M cells continue expressing CK18 during their movement from the crypt to the FAE.



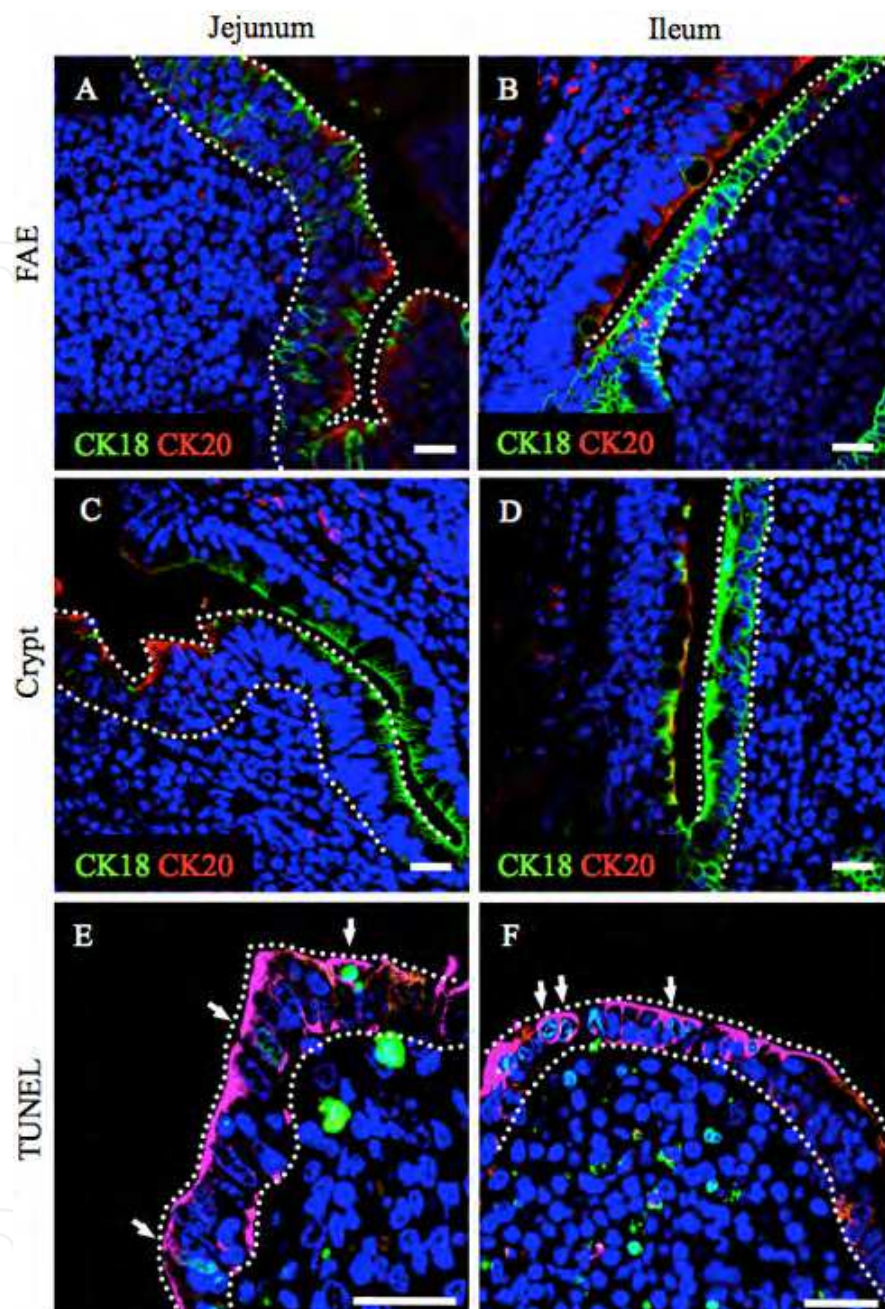


Fig. 5. Localization of CK18-, CK20-, and TUNEL-positive cells in the jejunum and ileum.

Jejunum and ileum sections were dual immunostained with anti-CK18 (IgG<sub>1</sub>) and CK20 (IgG<sub>2a</sub>) monoclonal antibodies. CK18 and CK20 were visualized by goat Alexa 488 anti-mouse IgG<sub>1</sub> (green) and by goat Alexa 594 anti-mouse IgG<sub>2a</sub> (red) antibodies (A-D). Apoptotic cells were detected with the Dead End Fluorometric terminal deoxynucleotidyl-transferase-mediated deoxyuridine-triphosphate-biotin nick-end labeling (TUNEL) system. The sections of jejunal and ileal FAE were stained using the TUNEL method and immunostained with anti-CK18 (IgG<sub>1</sub>) and CK20 (IgG<sub>2a</sub>) monoclonal antibodies. CK18 and CK20 were visualized by goat Alexa 546 anti-mouse IgG<sub>1</sub> (orange) and by goat Alexa 647

anti-mouse IgG<sub>2a</sub> (magenta) antibodies (E and F). Arrows show TUNEL-positive cells. Dotted lines show FAE. Bars = 10 μm.

3.4 Apoptosis of bovine M cells

It has been reported that M cells possibly transdifferentiate into enterocytes before exclusion from the FAE apex in the porcine small intestine (Miyazawa et al., 2006). To investigate these events for bovine intestinal M cells, we performed a triplicate CK18 and CK20, and TUNEL staining. The TUNEL-positive apoptotic cells were observed at the apical region of villi in both the jejunum and ileum (data not shown, see Hondo et al., 2011). We could also see TUNEL-positive signals in the apex of both jejunal and ileal FAE; however, TUNEL-positive apoptotic cells were only observed in CK20-positive cells (Figure 5E and F), indicating that only enterocytes could undergo apoptosis. Moreover, we quantified the cells that were positive for CK18, CK20 and apoptosis in the crypt-villus axis to evaluate the possibility that M cells transdifferentiate into enterocytes. The sections containing TUNEL-positive cells were selected, and the distance from the mouth of the crypt to the apex of half of the FAE was divided into thirds: lower, peripheral and apical regions. The proportions of CK18-positive cells in the lower region were 45 and 96% in the jejunal and ileal FAE, respectively, and these rates decreased to 21 and 57% at the apical regions of the FAE. On the other hand, the number of CK20-positive cells gradually increased from the lower region to the apex (Table 2). These data suggest that bovine M cells, positive for CK18, may transdifferentiate into CK-20 positive enterocytes before they undergo apoptosis at the apex of the FAE.

Regions	Marker	Cell No.	TUNEL+ Cell	CK18 (%) / CK20 (%)
Jejunum (n = 13)				
Total cell no./half FAE		91.5 ± 11.9		
Lower	CK18	13.9 ± 2.3	0	45.2 ± 54.8
	CK20	16.8 ± 2.4	0	
Peripheral	CK18	12.1 ± 3.0	0	39.2 ± 60.8
	CK20	18.4 ± 2.2	0	
Apical	CK18	6.5 ± 2.3	0	21.3 ± 78.7
	CK20	23.8 ± 3.1	1.9 ± 0.8	
Ileum (n = 10)				
Total cell no./half FAE		58.7 ± 6.2		
Lower	CK18	19.1 ± 1.8	0	96.1 ± 3.9
	CK20	0.8 ± 1.0	0	
Peripheral	CK18	18.3 ± 1.8	0	93.8 ± 6.2
	CK20	1.3 ± 1.7	0	
Apical	CK18	11.0 ± 2.6	0	57.2 ± 42.8
	CK20	8.2 ± 2.5	3.1 ± 0.7	

Table 2. Configurational comparison of CK18 and CK20-positive cells in jejunal and ileal FAE.

Results for cell no. and terminal deoxynucleotidyl-transferase-mediated deoxyuridine-triphosphate-biotin nick-end labeling (TUNEL)-positive cells are expressed as means ± SD; n, no. of cells. Results for cytokeratin (CK) 18/CK20 are expressed as the ratio of the proportion of CK18-positive cells to that of CK20-positive cells in each region of the FAE. The sections from jejunal and ileal follicle-associated epithelium (FAE) were stained with



anti-CK18 and anti-CK20 monoclonal antibodies and TUNEL. The sections containing TUNEL-positive cells were selected. One-half of the FAE was divided into thirds (lower region, from the mouth of crypt to the peripheral region; peripheral region, middle third of the FAE; and apical region, upper third of the FAE).

### 3.5 The expression of CK18 and CK20 in duodenum and colon

We investigated the expression patterns of CK18 and CK 20 in the duodenum and colon. In the duodenum, CK18 was also detected in the crypt. These CK18-positive cells moved to the villi and gradually changed CK18 for CK20 at the mouth of the crypts as observed in the crypt-villus axis of the jejunum and ileum (Figure 6). Besides this, prominent expression was also observed in Brunner glands of the duodenum (Figure 6A and B). In the colon, CK18-positive cells were observed in almost all crypt cells, and this was changed for the expression of CK20 at the mouth of the crypt (Figure 6C and D). This observation is similar to that for the mouse, indicating that CK18 and CK20 expression patterns are conserved across these species, except for the expression of CK18 in bovine M cells.

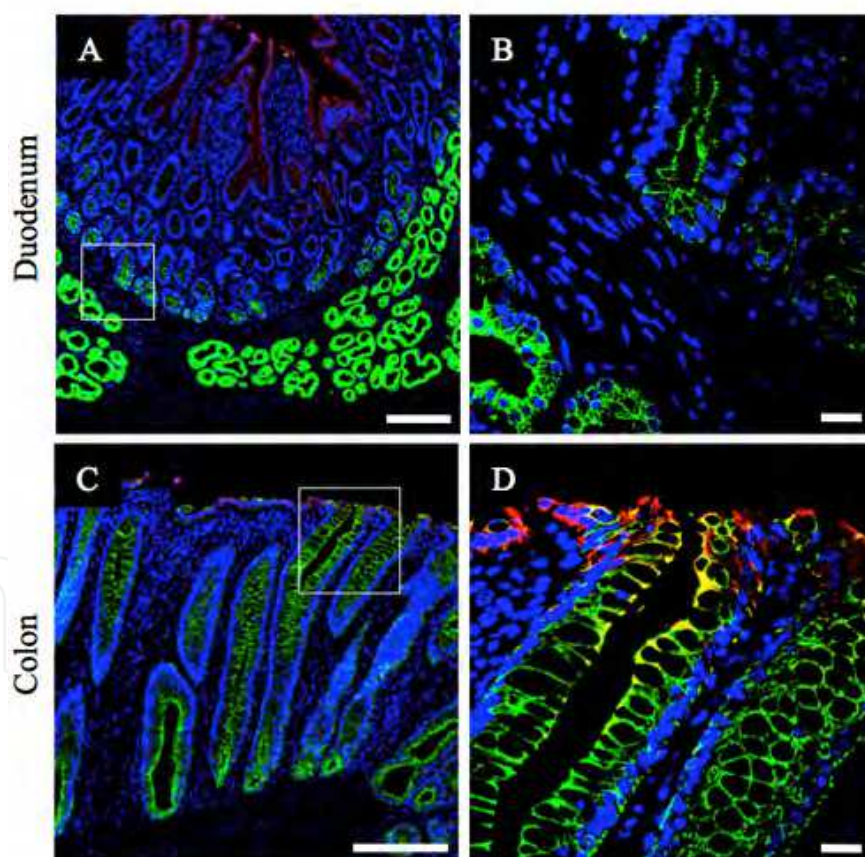


Fig. 6. CK18 and CK20 expression in the duodenum and colon.

Sections of duodenum (A and B) and colon (C and D) were dual immunostained with anti-CK18 (IgG<sub>1</sub>) and anti-CK20 (IgG<sub>2a</sub>) monoclonal antibodies. CK18 and CK20 were visualized by Alexa 488 goat anti-mouse IgG<sub>1</sub> (green) and Alexa 594 goat anti-mouse IgG<sub>2a</sub> (red)

antibodies, respectively. B and D are higher magnification of the boxes in A and C, respectively. Bars = 200  $\mu\text{m}$  (A and C) and 10  $\mu\text{m}$  (B and D).

#### 4. Conclusions

We have demonstrated that CK18 is expressed in bovine M cells, providing a useful tool for the detection of bovine intestinal M cells. Unlike some other mammals, ruminants develop two types of PPs in the jejunum and ileum, respectively, and both PP types possess different phenotypes for FAE and M cells. On the basis of this, we carefully observed the expression of CK18 in these M cells, and identified that both jejunal and ileal M cells were clearly detectable by immunohistochemistry of CK18. This method enabled us to detect an entire set of bovine M cells, and this will contribute to ongoing investigations of bovine M-cell differentiation and function.

Intestinal epithelial cells are well known to derive from stem cells located at the bottom of crypts (Barker and Clevers, 2010). Although M cells are an intestinal epithelial cell type, their origin has not been clarified; M cells directly differentiate from intestinal stem cells, or mature enterocytes, and convert into M cells under the influence of lymphocytes or microorganisms (Kerneis et al., 1997; Savidge et al., 1991). Recent analyses seem to support that M cells directly differentiate from stem cells, for example, Clevers *et al.* have shown that M cells derive from Lgr5-positive stem cells at the bottom of the crypt in the Lgr5-reporter mouse (Barker and Clevers, 2010). In the bovine intestine, proliferative cells, including the stem cell compartment and M cells, express CK18, indicating that CK18 expressed in immature cells continues into the M-cell lineage. Although these unique expression patterns are bovine specific, this aspect may help with clarifying the biological function of CK18 in intestinal epithelial cells. Our studies also confirm the possibility that M cells may transdifferentiate into enterocytes before apoptosis by examining the expression patterns of CK18 and CK20 in the crypt-FAE axis. Similar phenomena have been observed in murine and porcine M cells (Miyazawa et al., 2006; Sierro et al., 2000), indicating that this transdifferentiation of M cells into enterocytes is conserved for the M-cells of some species.

M cells are thought to be involved in the infections of various pathogens, such as pathogenic bacteria, viruses or prions (Brayden et al., 2005; Clark et al., 1998; Heppner et al., 2001; Takakura et al., 2011). In addition, we have recently demonstrated that bovine M cells possess a higher capacity for transporting the transmissible spongiform encephalopathies (TSE) agent than enterocytes *in vitro* (Miyazawa et al., 2010), suggesting a risk of bovine M cells as the entry site for some pathogens. The detection of bovine M cells by CK18 will contribute to the *in vivo* examination of the infectious mechanisms of various pathogens in the bovine intestine.

It is well known that different types of cells and tissues are characterized by the specific composition of their intermediate filaments. In the small intestine, CK7, CK8, CK18, CK19 and CK20 are expressed in epithelial cells (Flint et al., 1994; Kucharzik et al., 1998; Zhou et al., 2003). The subgroup of cytokeratins might serve as potent differentiation markers, because the diverse expression patterns of cytokeratins are correlated with epithelial differentiation (Moll et al., 1982). In the murine intestine, several CKs exhibit distinct expression patterns: CK7 and CK18 are strongly expressed in the crypt region, whereas

CK20 is expressed in differentiated epithelial cells lining the villi (Zhou et al., 2003). In this study, we have investigated the expression of various CKs in the bovine intestine, and demonstrated that CK18 and CK20 are expressed in the bovine intestinal tract. The expression of CK18 in the crypts and that of CK20 in villi were very similar to the expression patterns of mice. These conserved expression patterns of CK18 and CK20 indicate that these CKs are fundamental cytoskeletal proteins in intestinal epithelial cells. In addition, it has been reported that CK20 is important for keratin filament organization, and that both CK18 and CK20 have functional redundancy (Zhou et al., 2003). We observed that CK18 and CK20 did not co-localize throughout the FAE- or villus-crypt axis, implying important functional roles for CK18 and CK20 in the keratin filament formation in each compartment.

## 5. Acknowledgment

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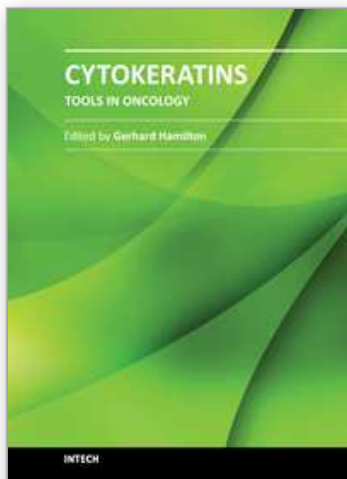


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Keratin 20 helps maintain intermediate filament organization in intestinal epithelia.  
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## **Cytokeratins - Tools in Oncology**

Edited by Dr. Gerhard Hamilton

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The first chapters of the volume "Cytokeratins - Tools in Oncology" discuss multiple functions of cytokeratins in organization of the intermediary filaments in normal intestine and liver as well as microfold L cells and the usability of cytokeratins 7, 8 and 20 in tumor diagnosis in detail. Epithelial to mesenchymal transition as a mechanism important in pathogenesis is touched in another chapter, followed by several articles dealing with the role of cytokeratins for detection of disseminated tumor cells and as response markers during chemotherapy. This book is therefore destined to all cancer researchers and therapists who want to understand the diagnostic application of cytokeratins in histology and, especially, the use of anti-cytokeratin antibodies to identify viable residual tumor cells accounting for a higher risk of tumor recurrence or cancer cells responding to chemotherapy, respectively.

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