

## Persorption of IgG-Fc-Coated Particulates from Intestinal Lumen into Portal Blood via Villous Columnar Epithelial Cells in Rat Small Intestine

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**ABSTRACT.** Previously, the specific antibody-mediated persorption of antigenic molecules and particulates from the small-intestinal lumen into the peripheral blood was clarified in rats, but the intermediation of the receptor for the specific antibodies was not. In this study, the existence of receptor for the specific antibody was experimentally examined in the rat small intestine. Glutaraldehyde-fixed sheep erythrocytes (SEs) coated by Fc-fragments of IgG (IgG-Fc), (Fab')<sub>2</sub>-fragments of IgG (IgG-Fab) or bovine serum albumin (BSA), were injected into 3 jejunal loops each 2 cm in length in non-orally pre-immunized rats, respectively. Thirty minutes after the injection, IgG-Fc-coated SEs were significantly more engulfed by villous columnar epithelial cells than Fab- or BSA-coated SEs. The most frequent absorption sites were the intestinal villous apices. The IgG-Fc-coated SEs were adhered to the striated borders and were engulfed by villous columnar epithelial cells. IgG-Fc-coated SEs passing through the epithelial cells were also detected in the subepithelial blood capillaries just beneath the villous epithelium, but not in the connective tissue and the lymph vessels. These findings suggest that the absorption of luminal antigenic particulates is probably mediated by the Fc-receptor, and that the absorbed antigenic particulates are directly transferred to the hepatic portal blood by passing through the endothelium of the subepithelial blood capillaries.

**KEY WORDS:** Fc receptor, particles, persorption, rat, small intestine.

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In many mammalian infants, intestinal epithelial cells absorb and transport molecules such as IgG from the maternal colostrum into systemic blood circulation [7, 11, 12, 17]. The absorption of IgG via intestinal epithelial cells ceases after weaning [13, 15, 16]. On the other hand, since orally ingested starch particulates were found in both the peripheral blood and urine of a dog in 1844 [8], many investigators have reported the phenomenon, *persorption*, by which macromolecules [14, 18, 25] or particulates [4, 24] are transported from the intestinal lumen to the peripheral blood circulation.

In adult rats, luminal IgG is absorbed from intestinal epithelial cells [28]. The IgG is engulfed and transported by endocytosis mediated by receptors on the intestinal

epithelial cells in young rats [19]. The mRNA for neonatal IgG-binding receptors (FcRns) gradually decreases until adulthood in rats [5]. However, FcRns remain on the intestinal epithelial cells in adult humans and probably mediate the transportation of IgG [3]. Our previous study suggested that luminal antigenic macromolecules and particulates are persorbed by the villous columnar epithelial cells at the late apoptotic stage, being mediated by the specific antibody in orally-immunized juvenile rats. In this study, we aimed to experimentally clarify the existence of epithelial receptor for particulates coated with Fc-fragments of rat IgG in the juvenile rat small intestine.

### MATERIALS AND METHODS

**Animals:** A total of 6 male Wistar rats aged 7 weeks (Japan SLC Inc., Hamamatsu, Japan) were maintained under conventional laboratory housing conditions. They were permitted free access to water and food (Lab MR Stock; Nosan Corp., Yokohama, Japan). The animal facility was maintained under conditions with a 12-hr light/dark cycle at

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$21 \pm 1^\circ\text{C}$  and 50–60% humidity. No signs of disorder were confirmed by clinical and pathological examinations of all animals. This experiment was approved by the Institutional Animal Care and Use Committee (Permission number: 14–09-01) and carried out according to the Guidelines for the Care and Use of Experimental Animals at Rokkodai Campus of Kobe University.

**Experimental protocol:** Three short loops queued up in a short length were made in the jejunum of each experimental rat. The first loop was injected with IgG-Fc-coated sheep erythrocytes (Fc-SEs) (Experiment-Fc). The second loop was injected with IgG-(Fab')<sub>2</sub>-coated SEs (Fab-SEs) (Experiment-Fab). The third loop was injected BSA-coated SEs (BSA-SEs) (Experiment-BSA) (Fig. 1).

**Preparation of SEs:** After the centrifugation (400 g for 10 min) of sheep blood (Nippon Biotest Lab., Tokyo, Japan), the sedimented SE-fraction from which the buffy coat had been removed was immersion-fixed with 2.5% glutaraldehyde in 0.1 M phosphate buffer (PB; pH 7.4) for 1 hr at room temperature (r.t.). The rinsed SEs were colorized by a peroxidase reaction using a 3,3'-diaminobenzidine (DAB; Dojindo Lab., Mashiki, Japan) solution containing 0.03% H<sub>2</sub>O<sub>2</sub> (DAB). Colorized SEs were rinsed and refixed in 2.5% glutaraldehyde in 0.1 M PB (pH 7.4) for 1 hr at r.t. After rinsing in PB, SEs were incubated with 0.1% rat IgG Fc (Cortex Biochem, San Leandro, CA, U.S.A.), 0.1% rat IgG (Fab')<sub>2</sub> (Seikagaku Corporation, Tokyo, Japan) or 0.25% BSA (Wako Pure Chemical Industries, Osaka, Japan) for 24 hr at r.t. After rinsing in PB, to prevent non-specific adherence of luminal materials, Fc-SEs and Fab-SEs were incubated with a 0.15% BSA for 24 hr at r.t. The rinsed SEs were suspended in phosphate buffered saline. The final concentration of SEs was adjusted to  $4 \times 10^6/\text{ml}$ . The strict binding of (Fab')<sub>2</sub> or Fc with the surfaces of SEs was confirmed by the agglutination test with anti rat IgG goat antibody (Jackson ImmunoRes. Lab., West Grove, PA, U.S.A.).

**Administration of SEs:** Under deep anesthesia with *i.p.* injection of pentobarbital sodium (Dainippon Sumitomo Pharma., Osaka, Japan), 3 jejunal loops, 2 cm in length, were prepared by closing both ends with sutures. Through a small abdominal incision, about 150  $\mu\text{l}$  of Fc-SEs, Fab-SEs

or BSA-SEs suspension were pre-warmed up to  $38^\circ\text{C}$  and injected into each jejunal loop from anti-mesenteric sides by means of a plastic syringe equipped with a 27-gauge needle. After the perfusion of SEs, the animals were settled in a warm and quiet chamber.

**Tissue preparation:** At 30 min after the injection, exsanguination was performed, and small tissue blocks were obtained rapidly from the jejunum, followed by immersion-fixation in periodate-lysine-paraformaldehyde (PLP) and Bouin's fixatives for 24 hr at  $4^\circ\text{C}$ . The tissue blocks were then dehydrated and embedded in paraffin and cut into 4- $\mu\text{m}$ -thick sections by routine procedures. They were mounted onto 3-aminopropyltriethoxysilane (Shin-Etsu Chemical, Tokyo, Japan)-coated glass slides. The PLP-fixed paraffin sections were stored at  $4^\circ\text{C}$  until use. Bouin's fixed and deparaffinized sections were stained with hematoxylin and eosin (HE).

**Detection of IgG:** After removal of endogenous peroxidase activity, the deparaffinized sections were treated with 1% normal rabbit serum for 1 hr at r.t. The sections were then incubated with anti-rat IgG goat IgG (diluted at 1:400; Jackson ImmunoRes. Lab.) for 20 hr at  $4^\circ\text{C}$ . Following incubation with anti-goat IgG rabbit antibody (diluted at 1:400; Jackson ImmunoRes. Lab.) for 1 hr at r.t., the sections were treated with goat peroxidase anti peroxidase complex (PAP) (diluted at 1:400; Jackson ImmunoRes. Lab.) for 1 hr at r.t. Finally, the sections were incubated with DAB and slightly counterstained with hematoxylin.

**Absorption frequencies of SE by intestinal epithelial cells:** The number of intraepithelial SEs was counted in 400 randomly selected intestinal villi that were centrally and longitudinally sectioned. SEs were easily distinguished from rat erythrocytes, because SEs were slightly smaller than rat erythrocytes and were colorized brown. The engulfed SEs were carefully distinguished from SEs that overlaid or underlaid the section under a light microscope using a 100 $\times$  objective lens. The mean number of intraepithelial SEs in Experiment-Fc was compared with that of Experiment-Fab or -BSA by Student's *t* test. *P* values less than 0.05 were considered statistically significant. Data are presented as means  $\pm$  standard deviations (SDs).

## RESULTS

**Absorption of SEs in the intestinal epithelium:** In all experimental groups, SEs were almost exclusively restricted to the central portion of the intestinal lumen, but a few SEs diffused into the mucous lining of the upper intervillous spaces.

In Experiment-Fc, relatively many Fc-SEs adhered to the striated borders of villous columnar epithelial cells in the apices of intestinal villi. Fc-SEs also adhered to the striated borders of a few middle-apical portions of intestinal villi that were in directly contact with Fc-SEs-containing luminal contents, because of the bending of intestinal villi by the pressure of the luminal contents. A few Fc-SEs were absorbed by the villous columnar epithelial cells, and passed through the side of the nucleus to the intercellular space (Fig.

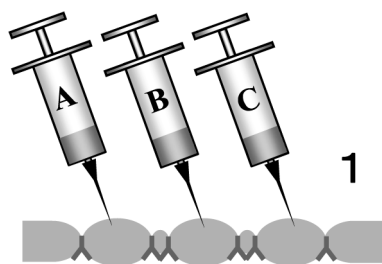


Fig. 1. Schematic drawing of the method of SEs-injection in jejunal loops. A, Fc-SEs suspension; B, Fab-SEs suspension; C, BSA-SEs suspension.

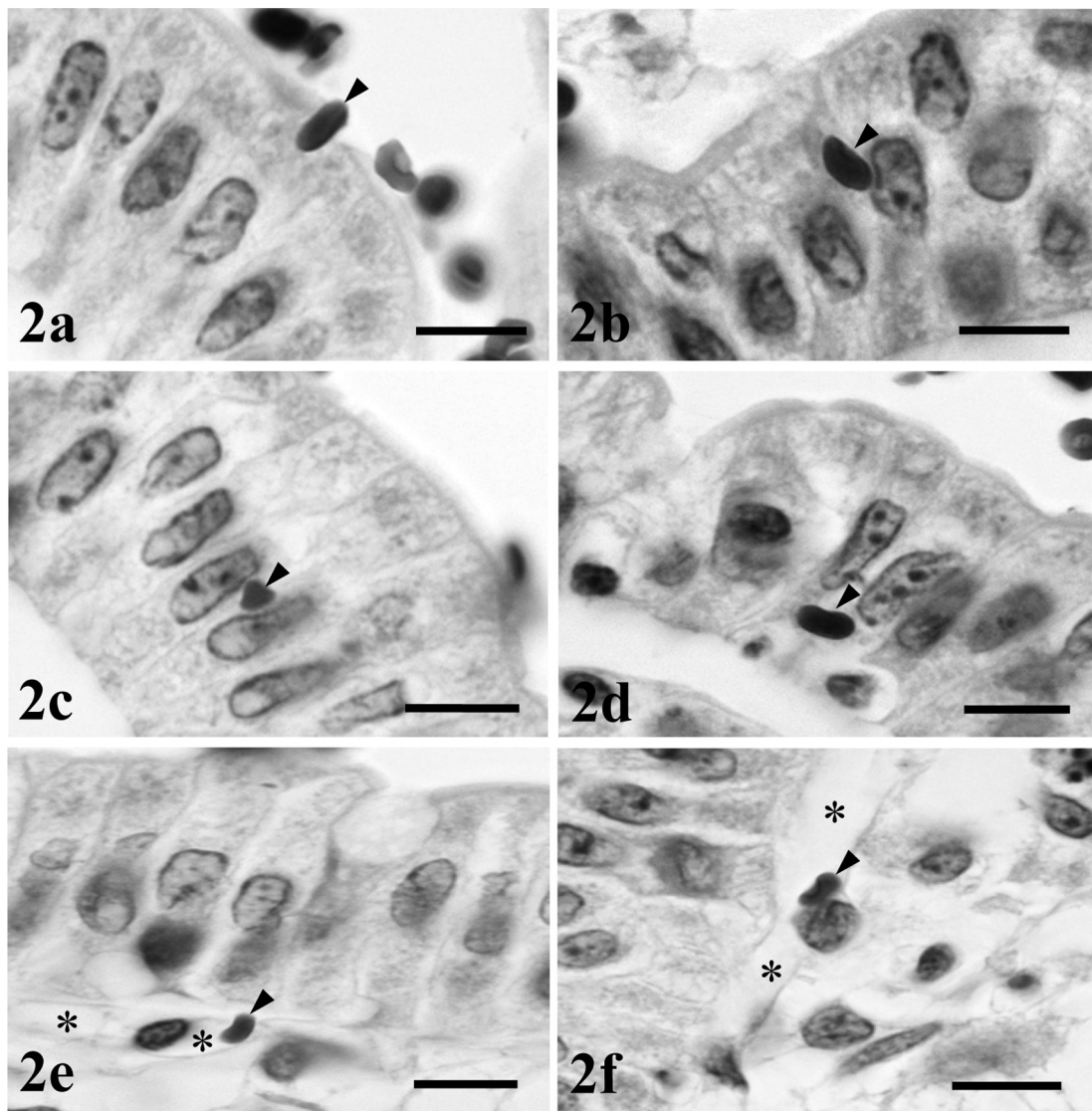


Fig. 2. High-magnification light micrographs of the absorption of Fc-SEs in intestinal villous apices of Experiment-Fc. Fc-SEs are engulfed by villous columnar epithelial cells (arrowhead in a), and pass through the side of the nucleus to the intercellular space (arrowheads in b-d). The apical shift of epithelial nuclei is clearly visible in (b). In the lamina propria, Fc-SEs pass through the endothelium of a subepithelial blood capillary (arrowhead in e) and enter the lumen of the subepithelial blood capillary (arrowhead in f). Asterisks indicate the lumina of subepithelial blood capillaries. HE staining. Bar=10  $\mu$ m.

2a-2d). In the lamina propria, Fc-SEs were never found in the matrix of connective tissue. However, Fc-SEs passing through the endothelium of the blood capillaries beneath the epithelium were occasionally found (Fig. 2e). Fc-SEs were also occasionally found in the blood capillaries beneath the epithelium (Fig. 2f), but never in the central lymphatics.

In Experiment-Fab and -BSA, SEs also adhered to the striated borders of villous columnar epithelial cells in the apices of the intestinal villi. But, the absorption of Fab- or BSA-SEs by villous columnar epithelial cells was seldom found. Fab- or BSA-SEs in the lamina propria including vasculatures were never found.

Table 1. Absorption frequencies of lumenally administered particulates by villous columnar epithelial cells in rat jejunum

Experimental group	Number of intraepithelial SEs <sup>a)</sup>
Experiment-Fc	12.5 $\pm$ 1.3*
Experiment-Fab	5.2 $\pm$ 1.0
Experiment-BSA	5.3 $\pm$ 1.6

Experiment-Fc: Injection of IgG-Fc-coated sheep erythrocytes.

Experiment-Fab: Injection of IgG-(Fab')<sub>2</sub>-coated sheep erythrocytes.

Experiment-BSA: Injection of BSA-coated sheep erythrocytes.

a) Mean number  $\pm$  SD of intraepithelial SEs in randomly selected 400 intestinal villi.

\* differs from Fab or BSA ( $P < 0.0001$ )



From histoplanimetry, the absorption frequency of Fc-SEs by villous columnar epithelial cells was significantly higher in Experiment-Fc than in Experiment-Fab or -BSA ( $P<0.0001$ ) (Table 1).

In all experimental groups, frequent exfoliation of epithelial cells was found in sites that were in contact with SEs (Fig. 3a-3b). In these sites, slight epithelial cytoplasmic vacuolation was only rarely observed in Experiment-Fab and -BSA, whereas high vacuolation was often found in Experiment-Fc. In Experiment-Fc, the condensation and apical shift of nuclei were markedly found in villous columnar epithelial cells in contact with Fc-SEs (Figs.

1b, 3c-3d). A few SEs were engulfed by villous columnar epithelial cells with nuclear condensation and the apical shift of nuclei, whereas SEs were rarely engulfed by vacuolated epithelial cells. In Experiment-Fc, Fc-SEs were often found in the cytoplasm of exfoliated epithelial cells (Fig. 3e-3f).

In Experiment-Fc, IgG-immunopositive expression was detected in the cytoplasm of the epithelial cells at the sites in contact with Fc-SEs. Strongly IgG-immunopositive expression was restricted to the lumina of blood capillaries and the central lacteal beneath the epithelial cells at the sites in contact with Fc-SEs in Experiment-Fc (Fig. 4).

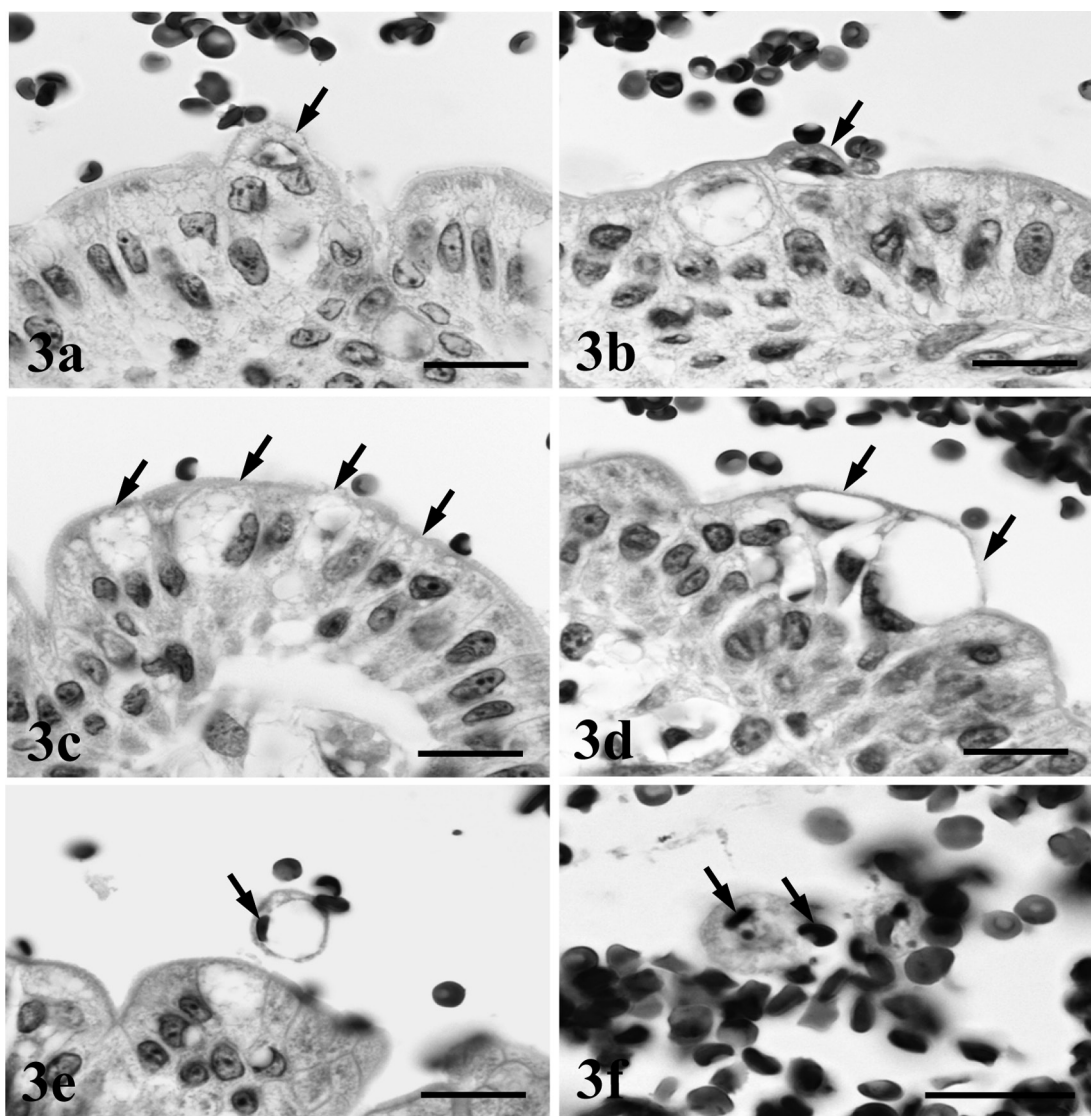


Fig. 3. High-magnification light micrographs of the epithelium in contact with the luminal contents in the intestinal villi. Exfoliation (arrows) and the shift of nuclei are visible in Experiment-Fab (a) and -BSA (b). SEs adhere to the exfoliating villous columnar epithelial cells. In Experiment-Fc, the cytoplasmic vacuolation and the apical shift of nuclei are marked (arrows in c-d). Nuclear condensation is also marked in (d). Fc-SEs are contained in the cytoplasm of exfoliated epithelial cells in Experiment-Fc (arrows in e-f). HE staining. Bar=10  $\mu$ m.

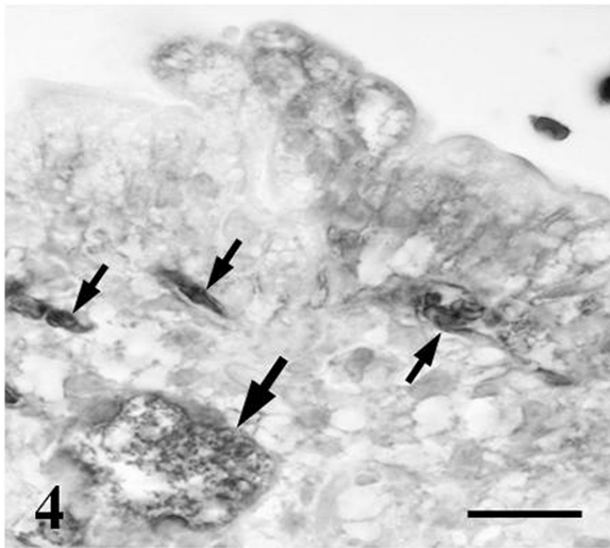


Fig. 4. In Experiment-Fc, the cytoplasm of the right-half epithelial cells exposed to the chyme containing the Fc-SEs expresses IgG-immunopositivity, while the cytoplasm of the left-half epithelial cells away from the chyme express negative. The lumina of the subepithelial blood capillaries (small arrows) and the central lacteal (large arrow) are also IgG-immunopositive. PAP method with slight hematoxylin counterstaining. Bar=10  $\mu$ m.

## DISCUSSION

The apoptotic process is induced in villous columnar epithelial cells, and accelerates during migration until they finally exfoliate from the apices of the intestinal villi [6, 20, 22, 23]. Several typical characteristics of apoptotic cells are DNA fragmentation, chromatin and nuclear condensation and the formation of apoptotic bodies [10]. Toward the apices of the rat intestinal villi and follicle-associated epithelium, the intensities of nuclear DNA fragmentation increase. Some epithelial nuclei with DNA fragmentation shift toward apical surfaces with the approach of the exfoliation site. In the intestinal villi that are bent by luminal pressure, DNA fragmentation has also been detected in the epithelium in contact with the chyme [2]. In the present study, the apical shift of nuclei, the condensation of nuclear chromatin and the exfoliation of epithelial cells were found in SE-adhered villous columnar epithelial cells. Therefore, the villous columnar epithelial cells in contact with the SE-containing chyme probably undergo local acceleration of epithelial apoptosis.

Apoptotic villous columnar epithelial cells actively absorb bovine lactoferrin in rats [21]. Antigenic macromolecules and particulates and their specific antibodies are also absorbed by epithelial cells at the late stage of apoptosis in orally pre-immunized rats [28, 29]. In the present study, the absorption of Fc-SEs was exclusively found in epithelial cells with morphological signs of apoptosis. In addition, epithelial cells in contact with Fc-SEs were exclusively IgG-immunopositive, and their neighbor subepithelial blood

capillaries and central lacteals were also IgG-immunopositive. These findings suggest that the progression of epithelial apoptotic processes is closely related with the absorption ability of IgG in rat villous columnar epithelial cells.

Orally administered BSA is absorbed from the villous columnar epithelial cells and passes through the blood vessels or the central lymphatics; the absorption quantity depends on the dosage of BSA in the adult rat intestine [25, 29]. On the other hand, duodenally administered BSA-SEs are histologically found in the blood vessels of the liver, but not in lymph vessels or mesenteric lymph nodes in orally pre-BSA-immunized rats. Therefore, the SEs taken up by epithelial cells are considered to be directly transported to the portal blood and finally reach the systemic blood circulation [28]. In the present findings, Fc-SEs passed through the endothelium of the subepithelial blood capillaries and were present in the capillary lumen, but not in the lymph vessels. This finding thus demonstrates the direct transportation of particulates from the intestinal lumen to the portal blood in rats.

In many mammalian infants, intestinal epithelial cells absorb and transport molecules such as IgG from the maternal colostrum into systemic blood circulation [7, 11, 12, 17]. Maternal IgG is endocytosed by the Fc receptor on the apical membranes of villous epithelial cells and is released into the subepithelial tissue in a pH-dependent manner [19]. Thus, the Fc receptor is probably committed to the absorption of IgG and immune complex from the intestine in infants. The IgG-absorption system in the neonatal phase gradually disappears as rats reach adulthood [5, 13]. However, FcRn is still expressed in intestinal epithelial cells in adult humans [3, 9], and IgG is absorbed by intestinal epithelial cells in adult rats [26]. Furthermore, the quantity of antigen absorbed from the intestinal lumen depends on the blood IgG concentration in Guinea pigs [1]. Intestinally administered HRP-containing endosomes are more evident in the epithelial cells of rats pre-immunized by HRP than in those of non-immunized rats [27]. In our previous study, the absorption of antigenic macromolecules and particulates by epithelial cells is mediated by their specific antibodies in orally pre-immunized rats [28, 29]. Thus, lumen-specific antibodies are deeply committed to absorption of luminal antigens in the rat small intestine. In the present study, Fc-SEs were significantly more engulfed by villous columnar epithelial cells than Fab-SEs or BSA-SEs in the rat small intestine. SEs were detected only in the blood capillary lumen beneath the villous epithelium in Experiment-Fc. Taken together, the present findings suggest that the absorption of luminal antigenic particulates is probably mediated by Fc-receptors, and that the absorbed antigenic particulates pass directly through the endothelium of blood capillaries to be transferred into the hepatic portal blood.

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