Selective Adherence of IgA to Murine Peyer's Patch M Cells: Evidence for a Novel IgA Receptor

Nicholas J. Mantis, Marsha C. Cheung, Koteswara R. Chintalacharuvu, Jacques Rey, Blaise Corthésy and Marian R. Neutra

*J Immunol* 2002; 169:1844-1851; doi: 10.4049/jimmunol.169.4.1844

http://www.jimmunol.org/content/169/4/1844

References

This article cites 43 articles, 18 of which you can access for free at: http://www.jimmunol.org/content/169/4/1844.full#ref-list-1

Why The JI? Submit online.

- Rapid Reviews! 30 days* from submission to initial decision
- No Triage! Every submission reviewed by practicing scientists
- Fast Publication! 4 weeks from acceptance to publication

*average

Subscription

Information about subscribing to *The Journal of Immunology* is online at: http://jimmunol.org/subscription

Permissions

Submit copyright permission requests at: http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts

Receive free email-alerts when new articles cite this article. Sign up at: http://jimmunol.org/alerts
Selective Adherence of IgA to Murine Peyer’s Patch M Cells: Evidence for a Novel IgA Receptor

Nicholas J. Mantis,2* Marsha C. Cheung,* Koteswara R. Chintalacharuvu, † Jacques Rey, ‡ Blaise Corthésy, † and Marian R. Neutra* M cells represent the primary route by which mucosal Ags are transported across the intestinal epithelium and delivered to underlying gut-associated lymphoid tissues. In rodents and rabbits, Peyer’s patch M cells selectively bind and endocytose secretory IgA (SlgA) Abs. Neither the nature of the M cell IgR nor the domains of SlgA involved in this interaction are known. Using a mouse ligated ileal loop assay, we found that monoclonal IgA Abs with or without secretory component, but not IgG or IgM Abs, bound to the apical surfaces of Peyer’s patch M cells, indicating that the receptor is specific for the IgA isotype. Human serum IgA and colostral SlgA also bound to mouse M cells. The asialoglycoprotein receptor or other lectin-like receptors were not detected on the apical surfaces of M cells. We used recombinant human IgA1 and human IgA2 Abs and domain swapped IgA/IgG chimeras to determine that both domains C1 and C2 are required for IgA adherence to mouse Peyer’s patch M cells. This distinguishes the M cell IgA receptor from CD89 (Fcγ/H9251) and the recently described Fcγ/H89900-057088 from the Swiss Science Research Foundation. DK34854 to the Harvard Digestive Diseases Center. B.C. is supported by Grant Award DK59295. M.R.N. is supported by National Institutes of Health Research secretory component; ASGPR, asialoglycoprotein receptor; Cy3, indocarbocyanine. 

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement

Received for publication April 12, 2002. Accepted for publication June 3, 2002.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 N.J.M. is supported by National Institutes of Health Mentored Research Scientist Award DK59295. M.R.N. is supported by National Institutes of Health Research Grants HD17557 and AI34757 and by National Institutes of Health Center Grant DK34854 to the Harvard Digestive Diseases Center. B.C. is supported by Grant 5200-057088 from the Swiss Science Research Foundation.

2 Address correspondence and reprint requests to Dr. Nicholas J. Mantis, Gastrointestinal Cell Biology Laboratory, Children’s Hospital, Boston, MA 02115; † Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA 90095; and ‡ Division of Immunology and Allergy, Hôpital Orthopédique, Lausanne, Switzerland

3 Abbreviations used in this paper: SlgA, secretory IgA; UEA-1, Ulex europaeus type I; TRITC, tetramethylrhodamine isothiocyanate; O-MALT, organized mucosa-associated lymphoid tissue; FAE, follicle-associated epithelium; plgR, polymeric IgR; SC, secretory component; ASGPR, asialoglycoprotein receptor; Cy3, indocarbocyanine.

Copyright © 2002 by The American Association of Immunologists, Inc.

0022-1767/02/0502.00

The Journal of Immunology
may express an IgA-specific receptor on their apical surfaces that mediates the transcytosis of SIgA and SIgA-Ag complexes.

Materials and Methods

Chemical and biological reagents

FITC- and tetramethylrhodamine isothiocyanate (TRITC)-conjugated streptavidin was obtained from Pierce (Rockford, IL). HRP conjugated to avidin was from Sigma-Aldrich (St. Louis, MO). The lectin *Ulex europaeus* type 1 (UEA-1) was obtained from Vector Laboratories (Burlingame, CA). Neoglycoproteins were purchased from EY Laboratories (San Mateo, CA). Paraformaldehyde (16% aqueous solution) and Epon 812-Araldite 502 embedding chemicals were purchased from Electron Microscopy Sciences (Warrington, PA). Mowiol was purchased from Calbiochem (San Diego, CA) and containing medium containing 1,2-dioctylcyclo-(2,2,2)-octane (Sigma-Aldrich) was made as described (17).

Igs and Ig labeling

Biotinylated mouse serum IgG was from Pierce. MOPC-315 (mouse IgG,s), TEPC-15 (mouse IgA,x), TEPC-183 (mouse IgM,x), MOPC-104e (mouse IgMA), human colostral IgA, and human serum IgA were purchased from Sigma-Aldrich. Purified human myeloma IgA1 and IgA2 were from Calbiochem. The generation and purification of recombinant human IgA1, IgA2 of the m-1 allotype (IgA2 m1), human IgA lacking the hinge region, IgG2, and IgG2 with CH1 of IgA1 have been previously described (18, 19).

Igs were biotinylated using EZ-link sulfo-NHS-LC-biotin (Pierce) or EZ-link LC-biotin-hydrazide (Pierce) following instructions provided by the manufacturer. Biotinylation was confirmed by dot blot analysis using streptavidin-HRP and an ECL detection kit purchased from Amersham Pharmacia Biotech (Piscataway, NJ). Protein concentrations were determined using the Bio-Rad protein assay reagent (Bio-Rad, Hercules, CA). Biotinylated Igs (0.8–1 mg/ml in PBS) were stored at –80°C until before use.

Mouse polymeric/dimeric IgA was purified from MB.2 hybridoma supernatant by size exclusion chromatography on a Sephacryl S300 column (2.6 × 100 cm) and conjugated to indocarbocyanine (Cy3) using Fluorolink (Amersham Pharmacia Biotech). Cy3-labeled polymeric/dimeric IgAa were mixed with recombinant SC produced in Chinese hamster ovary cells to reconstitute SIgA in vitro (20).

Animals

Mice and rats used in this study were housed under conventional specific pathogen-free conditions and were treated in strict compliance with guidelines established by Children’s Hospital of Boston (MA), Harvard Medical School (Boston, MA), and the National Institutes of Health (Bethesda, MD). Male Sprague–Dawley mice, 6–8 wk of age, were purchased from Charles River Breeding Laboratories (Wilmington, MA). Aavidolymphocyte receptor (ASGPR)-deficient mice carrying homozygous null mutations in the mouse hepatic lectin-2 subunit of the receptor (21) were purchased from The Jackson Laboratory (Bar Harbor, ME). IgA-deficient mice originally generated by Dr. G. Harriman (Baylor College of Medicine, Houston, TX) (22) were a gift from Dr. J. Nedrud (Case Western Reserve University, Cleveland, OH). Sprague Dawley mice were obtained from Taconic Farms (Cleveland, OH). Sprague Dawley mice were obtained from Taconic Farms (Cleveland, OH). Sprague Dawley mice were obtained from Taconic Farms (Cleveland, OH). Sprague Dawley mice were obtained from Taconic Farms (Cleveland, OH).

Ligated ileal loop assays and processing of Peyer’s patch tissues

Mouse ligated ileal loop assays were done as previously described (15). During the procedure mice were maintained under averitin (5 g tri-bromo-ethanol in 2.5 ml t-amyl alcohol; 200 mg/kg animal weight) anesthesia and kept warm on a 37°C warming pad. Biotinylated Abs were injected into ligated ileal loops at a concentration of 100 μg/ml, unless noted otherwise. M cells were labeled in vivo by coinjection of TRITC-labeled UEA-1 (20 μg/ml). At the completion of the experiment, the mice were sacrificed by cervical dislocation and Peyer’s patches were removed, gently washed in PBS to remove unbound Abs, then immersed in paraformaldehyde (4% w/v in PBS). Whole, fixed Peyer’s patches were labeled with streptavidin-FITC (20 μg/ml) to detect bound biotinylated Igs, then cryosectioned using a Leica cryostat model CM3050 (Leica, Nussloch, Germany). Sections were captured on Superfrost microscope slides (Fisher, Pittsburgh, PA) and coverslips were labeled with streptavidin. The labeled sections were mounted with glycerol (20). Alternatively, freshly isolated Peyer’s patches tissues were fixed in paraformaldehyde (4% w/v in PBS) and embedded in Epon-Araldite, as described previously (23). Epon-Araldite blocks were sectioned using glass knives mounted on a Leica Ultracut E microtome. Semithin plastic sections (0.5–1 μm) were etched with melting solution and labeled with streptavidin-FITC (2 μg/ml) and UEA-1 TRITC (2 μg/ml) (23).

Immunolabeling rat liver and intestinal tissues

Freshly excised rat Peyer’s patch or liver tissue samples were embedded in Tissue-Tek O.C.T. (Sakura FineTek, Torrance, CA) in plastic base molds (Curtin Matheson Scientific, Houston, TX), then snap-frozen in liquid nitrogen-cooled isopentane. Acetone-fixed, frozen sections (5–7 μm) of rat liver or Peyer’s patch were labeled with polyclonal rabbit anti-rat ASGPR antiserum (kindly provided by Dr. D. Alpers, Washington University, St. Louis, MO (24)) or control nonimmune serum, followed by biotinylated goat anti-rabbit IgG (Southern Biotechnology Associates, Birmingham, AL) and streptavidin-FITC.

Immunolabeling human intestinal tissues

Paraffin sections of pediatric ileal biopsies were obtained from the Children’s Hospital Department of Pathology after approval by the Children’s Hospital Internal Review Board. Sections (5 μm) were deparaffinized, blocked for 1 h in PBS containing goat serum (2% v/v), and stained with biotin-labeled, affinity-purified goat anti-human IgA, IgG, or IgM Abs (ICN Pharmaceuticals, Costa Mesa, CA) followed by streptavidin-FITC.

Microscopy

Tissue sections were viewed using a Zeiss Axiosphemat microscope (Carl Zeiss, Thornwood, NY) equipped for epifluorescence or a Bio-Rad MRC1024 confocal microscope (Bio-Rad). When using the Zeiss Axiosphemat, images were either photographed using a 35-mm camera and Kodak Elite Chrome 400 film (Kodak, Rochester, NY) or collected electronically using a SPOT digital camera (Diagnostic Instruments, Sterling Heights, CA). When using the MRC1024 confocal microscope, images were collected electronically using software provided by the manufacturer. Electronic images were edited and annotated using Adobe Photoshop (Adobe Systems, Mountain View, CA).

Results

Ig binding to the apical surfaces of mouse Peyer’s patch M cells is IgA specific

We began by establishing a convenient model for studying the interaction of Igs with M cells. To confirm IgA binding in this model, mouse hybridoma IgA TEPC-15 (mouse IgA,x) or MOPC-315 (mouse IgA,x) were biotinylated and injected into BALB/c mouse ligated ileal loops containing Peyer’s patches. After 40 min the Peyer’s patches were removed, fixed, and frozen or embedded in EPON. Frozen thick sections or semithin EPON sections were labeled with streptavidin-FITC to detect biotinylated IgA. Both monoclonal IgA Abs irrespective of L chain identity bound to the apical surfaces of most M cells within the Peyer’s patch FAE (Fig. 1B). M cells were identified by phase contrast microscopy (Fig. 1A) and by containing with the lectin UEA-1 (Fig. 1, C and D). Neither monoclonal IgA Ab bound to adjacent FAE enterocytes or villus enterocytes, although both Abs occasionally associated with the mucus layer overlying the FAE and villus epithelium (data not shown).

To determine the isotype specificity of Ig recognition by M cells, mouse monoclonal IgM Abs TEPC-183 and MOPC-104e, and mouse polyclonal serum IgG, were biotinylated and tested in the ligated ileal loop assay. While IgA bound to Peyer’s patch M cells (Fig. 2A), neither IgG nor IgM adhered to the FAE (Fig. 2, C and D), even when these Igs were injected into
IgA binding to Peyer’s patch M cells is not mediated by the ASGPR

Two receptors with IgA binding capacity have been reported on rodent intestinal epithelium in vivo: the pIgR and the ASGPR. Expression of pIgR is largely restricted to crypt epithelial cells and is not present on the FAE (11–15). The ASGPR, first identified on the sinusoidal membranes of hepatocytes, is a lectin-like receptor that can bind IgA via oligosaccharide side chains bearing terminal galactose residues (26, 27). ASGPR has been detected on the apical surfaces of certain human colonic epithelial cell lines in vitro (28) and on the luminal surfaces of rat neonatal (but not adult) enterocytes in vivo (24), although its function on enterocytes remains unknown. Because it has been previously reported that rat Peyer’s patch M cells bind IgA (15), we used available rabbit anti-rat ASGPR antiserum and immunofluorescence microscopy to examine whether the ASGPR is expressed on the apical surfaces of M cells in the FAE of Peyer’s patches. Anti-ASGPR antiserum failed to label either the villus epithelium or FAE on frozen sections of rat Peyer’s patch (Fig. 4). The specificity and activity of the anti-ASGPR antiserum was confirmed on sections of rat liver where the antiserum labeled hepatocyte sinusoidal membranes, consistent with the known distribution of ASGPR (Fig. 4).

IgA RECEPTOR ON PEYER’S PATCH M CELLS

Selective adherence of IgA to the apical surfaces of mouse Peyer’s patch M cells. Biotinylated mouse monoclonal IgA Ab TEPC-15 (100 μg/ml) and TRITC-labeled UEA-1 (20 μg/ml) were coinjected into a BALB/c ligated ileal loop containing a single Peyer’s patch and incubated for 40 min. A plastic 1-μm section of Peyer’s patch was labeled with streptavidin-FITC and visualized by phase contrast (A) and fluorescence (B–D) microscopy. A. Phase contrast image shows FAE and villus epithelium (upper left). When in the proper plane of section (arrowhead), M cells can be identified morphologically by their abbreviated apical membrane and the clusters of lymphocytes in their intraepithelial pockets. B. The same section viewed by fluorescence microscopy shows that IgA adhered to a subpopulation of cells within the FAE, but not to cells in villus epithelium. C. UEA-1 identifies M cells within the FAE. D. Merge of B and C demonstrates colocalization of IgA and UEA-1 on the apical surfaces of M cells (arrowhead).

Mouse Peyer’s patch M cells bind and endocytose SlgA

We wished to test whether binding of SlgA to the apical surfaces of M cells results in Ab transcytosis, as was previously proposed by Weltzin et al. (15). To visualize IgA directly and with greater sensitivity, purified mouse monoclonal IgA consisting exclusively of dimers and higher m.w. polymers was labeled with Cy3 and associated in vitro with recombinant SC. Cy3-labeled SlgA Abs were injected into BALB/c mouse ligated ileal loops and visualized on frozen Peyer’s patch tissue sections by confocal laser scanning microscopy. Forty minutes after inoculation, Cy3-SlgA Abs were detected on the apical surfaces of Peyer’s patch M cells and within M cell intracellular vesicles (Fig. 3, A and B). Intracellular vesicles containing SlgA were located apically, clustered near the intraepithelial pocket membrane, and along the basolateral membranes. In some cases, SlgA was present in M cell basal processes that extend through the basal lamina (Fig. 3C) (23). These data indicate polymeric SlgA can adhere to M cell surfaces and be transported across the FAE.
However, we could not exclude the possibility that the ASGPR is present on the apical surfaces of M cells at low levels not detectable by immunohistochemistry. We predicted that if the ASGPR is the IgA receptor on Peyer’s patch M cells, then IgA binding to M cells would be abolished in ASGPR-deficient mice (21). Using the ligated ileal loop assay in ASGPR knockout mice, we found that IgA, but not IgM, accumulated on the luminal surfaces of Peyer’s patch FAE with a pattern indistinguishable from that observed in normal mice (data not shown). Thus, we conclude that the ASGPR is not the receptor that mediates binding of IgA to the apical surfaces of M cells.

We also tested the possibility that IgA may bind via its carbohydrate moieties to other lectin-like receptors on M cells. Although no specific lectins have been identified on M cells, lectin-like receptors are widespread on mammalian cells (29). Mouse IgA contains two N-linked oligosaccharide side chains terminating in mannose, galactose, N-glycolyseraminic acid, or N-acetylglycosaminic acid (30). To test whether IgA oligosaccharides are important for M cell binding, IgA was biotinylated either before or after treatment with sodium periodate to disrupt monosaccharides containing vicinal hydroxyl groups and destroy most carbohydrate epitopes (31). Periodate-treated IgA bound to the M cells in the BALB/c mouse with a pattern identical to untreated IgA (data not shown). To detect the possible presence of lectin-like receptors on M cells, we examined whether other glycoproteins with terminal galactose or mannose residues, including asialofetuin, asialoorosomucoid, BSA-galactose, BSA-mannose, or BSA-glucose, bound to M cells. No binding of any of these glycoproteins (tested at concentrations ranging from 10 to 1000 μg/ml) to M cells was detected in the BALB/c ligated ileal loop assay (data not shown). These data argue against the presence of a lectin-like receptor on the apical surfaces of M cells involved in binding IgA.

**Domains Ca1 and Ca2 are important for IgA binding to mouse Peyer’s patch M cells**

Identification of the domains of IgA that are important for M cell binding could provide clues as to the nature of the IgA receptor. Human IgA is comprised of two subclasses, IgA1 and IgA2 (32). The primary difference between the two subclasses is that IgA1 has a heavily O-glycosylated 16-aa hinge region located between domains Ca1 and Ca2, whereas IgA2 has a 3-aa hinge that is not glycosylated. Excluding the hinge, the protein sequence of human IgA1 and IgA2 differ in only 14 aa scattered along the polypeptide (32). To determine whether both classes of human IgA bind to mouse M cells, purified myeloma IgA1 and IgA2 were biotinylated and tested in the ligated ileal loop assay. We observed that human IgA2 bound to mouse M cells but human IgA1 did not (Fig. 5, A and B). The same result was obtained when recombinant human glycosylated IgA1 and IgA2 produced by mouse Sp2/O myeloma cells were tested (data not shown). This differentiates the M cell IgA receptor from CD89 (FcαRI), a receptor on human myeloid-derived cells that recognizes IgA1 and IgA2 with equal affinity (33).

We hypothesized that the inability of IgA1 to bind to mouse M cells could be due to the presence of the 16-aa hinge located between Ca1 and Ca2. To test this we used recombinant IgA1 molecule lacking the hinge (IgA1Δhinge) that was otherwise fully glycosylated (18). In the BALB/c ligated ileal loop assay, IgA1Δhinge adhered to the apical surfaces of Peyer’s patch M cells (Fig. 5, C–F). Furthermore, a recombinant Ig containing Ca1 of IgA2 fused to the IgG2 hinge and Cγ2 and Cγ3 domains did not bind (Fig. 6), indicating that the IgA Ca1 domain alone is not

**FIGURE 3.** Binding and transepithelial transport of SIgA by Peyer’s patch M cells. Cy3-labeled mouse monoclonal SIgA (100 μg/ml) was injected into BALB/c ligated ileal loops containing a single Peyer’s patch and incubated for 40 min. Frozen sections (5–7 μm) of fixed tissue were viewed by confocal microscopy. A, SIgA was present within M cells and concentrated on M cell apical surfaces. B, In some M cells, SIgA was visible in apical vesicles, on lateral membranes (arrowhead), and on the membrane lining the intraepithelial pocket. C, SIgA was also detected in M cell processes (arrowheads) that extend through the basal lamina.

**FIGURE 4.** ASGPR is expressed on rat hepatocytes but not on Peyer’s patch FAE. Frozen sections of rat liver (A and B) or Peyer’s patch (C and D) were labeled with rabbit anti-rat ASGPR antiserum (A and C) or control nonimmune serum (B and D) as described in Materials and Methods and viewed by confocal microscopy. A, Anti-ASGPR Abs labeled sinusoidal membranes in liver sections. B, Control serum did not label hepatocytes. Neither anti-ASGPR antiserum (C) nor control serum (D) labeled Peyer’s patch FAE or villus epithelium (VE).
sufficient to mediate Ig binding to M cells. Taken together these results suggest that the IgA-M cell interaction requires both C/H9251 and C/H9251/2 domains in a well-defined spatial conformation, and that the inability of human IgA1 to bind to mouse M cells is due to the extended hinge.

IgA is present on the apical surfaces of M cells from the human ileum

In adult and neonatal rabbit Peyer’s patches and appendices, endogenous SLgA can be detected on the apical surfaces of M cells by immunohistochemistry (8–10). To determine whether endogenous SLgA is present on the apical surfaces of human M cells, paraffin sections of normal pediatric terminal ileum containing organized lymphoid follicles were stained with affinity-purified, goat anti-human IgA Abs. Anti-IgA Abs labeled plasma cells in the lamina propria (Fig. 7A) and occasionally in lymphoid follicles (data not shown). Anti-IgA Abs also stained some (but not all) M cell membranes in biopsies from three different individuals (Fig. 7, B and C). M cells were identified by morphological criteria. Affinity-purified anti-IgM Abs or irrelevant control Abs did not label M cells (data not shown). These results suggest that human M cells, like those in rabbits and rodents, express a receptor for IgA.

Discussion

M cells are the primary route through which particulate Ags, soluble macromolecules, and pathogens are delivered from the intestinal lumen to inductive sites of the mucosal immune system. Adherence to the apical surfaces of these specialized epithelial cells is a prerequisite for efficient transepithelial transport. Therefore, identification of potential mediators of M cell adherence is central to understanding mucosal immune responses. In this paper we confirmed that IgA, with or without associated SC, selectively adheres...
domains C\textsubscript{1} and C\textsubscript{2} relative to each other such that the M cell receptor recognizes the C terminus of C\textsubscript{3} (37, 38). We postulate that the extended hinge of IgA\textsubscript{1} may interfere with binding by altering the spatial arrangement between C\textsubscript{1} and C\textsubscript{2} relative to each other such that the M cell receptor cannot simultaneously contact both domains. Alternatively, the O-linked oligosaccharide side chains branching from the IgA\textsubscript{1} hinge (32) could potentially mask adjacent amino acids on C\textsubscript{1} or C\textsubscript{2} that are important for receptor recognition.

Although the data presented in this paper suggest that the protein responsible for binding SIgA on the apical surfaces of M cells is novel and distinct from previously described human and murine Fc\textsubscript{R}s, this conclusion is premature in the absence of the additional molecular information. For example, a recently described Fc\text{omR} has been shown by in situ hybridization and RT-PCR to be expressed at high levels in the small intestine (16, 39). Although the expression of this receptor was originally thought to be restricted to B cells and macrophages, it has been now been reported to be present on mesangial cells (40). In light of these studies we cannot exclude the possibility that an alternative form of this receptor (which binds IgA but not IgM) could be expressed on M cells. Future studies in this laboratory will be aimed at identifying the M cell IgA receptor using molecular genetic and biochemical techniques.
The function of the IgA receptor on M cells may be to mediate the delivery of SlgA from the intestinal lumen to underlying O-MALT. Consistent with this, we observed that SlgA applied to the apical surfaces of M cells accumulated within vesicles clustered near the intraepithelial pocket membranes. Presumably these vesicles were released into the pocket. SlgA also accumulated in M cell basolateral processes that have been proposed to make direct contact with subepithelial leukocytes (23). Following M cell transcytosis, SlgA-Ag complexes could be sampled by pocket B lymphocytes (6) and/or subepithelial dendritic cells (7). Brandtzaeg et al. (41) have hypothesized that memory B cells in the M cell pocket present luminal Ags to neighboring resident T cells, promoting T cell survival and B cell differentiation. Human and murine mature B cells express an FcεRI that can mediate endocytosis of both IgA- and IgM-immune complexes (39), although it has not been determined whether B cells within the M cell pocket express this receptor. SlgA-immune complexes could also interact with dendritic cells that form a dense network below the FAE and occasionally migrate into the M cell pocket (7). In vitro, human monocyte-derived DC can bind and internalize SlgA (42, 43).

In this report we detected IgA on the apical surfaces of M cells in the human pediatric ileum, suggesting that human M cells, like those in the rabbit and mouse, bind and endocytose SlgA. This could have implications for understanding the regulation of mucosal immune responses in humans and potential applications for the development of oral vaccine delivery strategies. In humans a significant proportion of the intestinal microflora is coated with SlgA (44). This raises the possibility that M cells may “sample” IgA-coated commensal bacteria, promoting the maintenance of antimicrobial immune responses that could control the luminal microflora and prevent microorganisms from the mucosa (2). There is currently interest in targeting vaccines to the apical surfaces of M cells in the human small intestine, colon, and rectum. In mice, exogenous IgA has been used as an Ag delivery vehicle, apparently promoting the sampling of oral or rectal vaccines by M cells and more efficient delivery to the mucosal immune system (45, 46). A better understanding of the interaction of SlgA with M cells and the resulting immune response is needed to assess the feasibility of such a vaccine strategy in humans.

Acknowledgments

We thank Drs. David H. Alpers (Washington University) and Anne Hubbard (Johns Hopkins University, Baltimore, MD) for providing us with anti-ASGPR antisera, and Dr. Kamren Badizagidgen (Children’s Hospital) for obtaining paraffin sections of pediatric ileum. We thank Dr. John Nedrud for providing us with IgA-deficient mice and Dr. Mary Petzke for help in maintaining the colony. We also acknowledge Lynn Sosa for performing the neoglycoprotein binding assays.

References


