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Human Intestinal Epithelial Cells Express a Novel Receptor for IgA[1]

Tetsuro Kitamura,* Roberto P. Garofalo,[2]* Atsushi Kamijo,* Dianne K. Hammond,* Janet A. Oka,† Carlton R. Caflisch,* Mohan Shenoy,* Antonella Casola,* Paul H. Weigel,† and Randall M. Goldblum*

Binding and transport of polymeric Igs (pIgA and IgM) across epithelia is mediated by the polymeric Ig receptor (pIgR), which is expressed on the basolateral surface of secretory epithelial cells. Although an Fc receptor for IgA (FcαR) has been identified on myeloid cells and some cultured mesangial cells, the expression of an FcαR on epithelial cells has not been described. In this study, binding of IgA to a human epithelial line, HT-29/19A, with features of differentiated colonic epithelial cells, was examined. Radiolabeled monomeric IgA (mIgA) showed a dose-dependent, saturable, and cation-independent binding to confluent monolayers of HT-29/19A cells. Excess of unlabeled mIgA, but not IgG or IgM, competed for the mIgA binding, indicating that the binding was IgA isotype-specific and was not mediated by the pIgR. The lack of competition by asialoorosomucoid and the lack of requirement for divalent cations excluded the possibility that IgA binding to HT-29/19A cells was due to the asialoglycoprotein receptor or β-1,4-galactosyltransferase, previously described on HT-29 cells. Moreover, the FcαR (CD89) protein and message were undetectable in HT-29/19A cells. FACS analysis of IgA binding demonstrated two discrete populations of HT-29/19 cells, which bound different amounts of mIgA. IgA binding to other colon carcinoma cell lines was also demonstrated by FACS analysis, suggesting that an IgA receptor, distinct from the pIgR, asialoglycoprotein receptor, galactosyltransferase, and CD89 is constitutively expressed on cultured human enterocytes. The function of this novel IgA receptor in mucosal immunity remains to be elucidated. ***The Journal of Immunology*****, 2000, 164: 5029–5034.**

Immunoglobulin A is the most prominent class of Ab in intestinal tissue and mucosal secretions. A better understanding of IgA-mediated mucosal immunity requires insights into the interaction between IgA and receptors present at mucosal surfaces (1–4). In particular, the high concentrations of IgA on either side of the mucosal epithelium might have immunomodulatory effects on intestinal epithelial cells.

Receptors that bind human IgA have been demonstrated on numerous cell types and on some bacteria. The best characterized of these is the receptor for Fc fragments of IgA (FcαR, CD89), which is expressed on myeloid cells including neutrophils (5–7), monocytes (8–11), macrophages (12–14), and eosinophils (15). The asialoglycoprotein receptor (ASGPR)[3] found on hepatocytes, some macrophages, and recently demonstrated on cultured intestinal epithelial cells (16, 17), and β-1,4-galactosyltransferase expressed on plasma membranes (18) can also act as a cell-surface receptor for different forms of IgA. The polymeric Ig receptor (pIgR), expressed on secretory epithelium binds J chain-containing IgA polymers and IgM. Both B and T lymphocytes have been shown to bind IgA, but a receptor has not been fully characterized (19, 20). Expression of CD89 by cultured rat and human mesangial cells has been described (21). However, our recent studies suggest that another, as yet uncharacterized IgA receptor is constitutively expressed on mesangial cells (22). The function of this receptor may be related to its ability to initiate intracellular signals, leading to cellular activation.

HT-29, a well-characterized human cell line derived from a colonic adenocarcinoma, expresses pIgR on its surface (23). In the present study, we demonstrate that HT-29 clone 19A and other human colonic cell lines constitutively express a novel IgA receptor. The characteristics of this receptor are similar to those we have described on mesangial cells, but distinct from any IgA receptor previously described on epithelial or other cell types.

Materials and Methods

Intestinal epithelial cell lines

HT-29 clone 19A (HT-29/19A), a colonic adenocarcinoma cell line, was kindly provided by Dr. Andrew Morris (Baylor College of Medicine, Houston, TX). This clone was derived by sodium butyrate treatment of HT-29 cells and exhibits features of differentiated colonic epithelial cells, independent of the presence of glucose (24). The parent cell line HT-29 and the human colonic T84 and Caco 2 cells were obtained from American Type Culture Collection (Manassas, VA). Cells were cultured in DMEM, supplemented with 10% FCS, 2 mmol/L L-glutamine, 1 mmol/L sodium pyruvate, 50 μg/ml streptomycin, and 50 U/ml penicillin. T84 cells were grown in DMEM/F12 medium supplemented with 5% FCS. All cell lines were maintained at 37°C in 5% CO_2. All tissue culture reagents were purchased from Life Technologies (Gaithersburg, MD).

Ig preparations and reagents

Monomeric IgA1 (mIgA) was prepared in our laboratory as previously described (22). Briefly, IgA1 fraction was isolated from normal donors'

*Department of Pediatrics, University of Texas Medical Branch, Galveston, TX 77555; and †Department of Biochemistry, University of Oklahoma Health Science Center, Norman, OK 73190

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[2] Address correspondence and reprint requests to Dr. Roberto P. Garofalo, Department of Pediatrics, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0369. E-mail address: Roberto.garofalo@UTMB.edu

[3] Abbreviations used in this paper: ASGPR, asialoglycoprotein receptor; AIgA, heat-aggregated monomeric IgA; mIgA, monomeric IgA; pIgR, polymeric Ig receptor; S-IgA, secretory IgA; ^{125}I-mIgA, ^{125}I-labeled mIgA.

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sera by Jacalin affinity chromatography. Serum was diluted with PBS (pH 7.1), filtered through a 0.2-μm filter (Corning Glass Works, Corning, NY), and chromatographed on columns of Jacalin immobilized on cross-linked 6% beaded agarose (Pierce, Rockford, IL). After washing the column with PBS, IgA1 was eluted with 0.2 M melibiose (Sigma, St. Louis, MO) in PBS and concentrated by ultrafiltration using 30,000 m.w. exclusion membranes (Centriprep 30; Amicon, Beverly, MA). The IgA1 was then fractionated into three peaks by HPLC molecular sieve chromatography, using a 1.5 × 30 cm Superdex HR 200 column (Pharmacia Biotech, Piscataway, NJ). The IgA1 fraction, found to be 98% pure by SDS-PAGE and densitometry of Coomassie-stained gels, was used for radiolabeling. Some mIgA was heat-aggregated (AIgA) by incubation for 150 min at 63°C, as previously described (21, 22). Human IgG, secretory IgA (S-IgA), BSA, and asialoorosomucoid were purchased from Sigma. Purified serum IgM and IgA was obtained from Pierce. mIgA2 was isolated from the later by removing all IgA1 by Jacalin affinity chromatography. Biotinylation of mIgA or AIgA was performed using EZ-Link NHS-Biotin (Pierce) according to the manufacturer's instruction.

Binding of radiolabeled IgA1 to HT-29/19A cells

mIgA was radiolabeled with $Na^{125}I$ (10–20 mCi/μg iodine) (Amersham, Arlington Heights, IL), as previously described (25). Confluent monolayers of HT-29/19A cells were washed once in PBS and incubated 30 min in DMEM without serum. The cells were then transferred to ice, washed twice with PBS, and incubated for 60 min with ^{125}I-labeled mIgA (^{125}I-mIgA) (2 μg/ml) in 0.2 ml of PBS (without divalent cations) alone or in the presence of various concentrations of nonradioactive mIgA, AIgA, S-IgA, IgG, IgM, or asiasoorosomucoid. The radioactive medium was removed and the cells were rapidly washed three times with HBSS. The cells were solubilized in 0.3 N NaOH (0.4 ml) and the lysates were transferred to gamma tubes and the radioactivity was quantified in a Packard 5002 gamma counter (Downers Grove, IL). The protein content of the lysates was measured by the Bradford's method using BSA as the standard. Assays were performed in duplicate and the data were analyzed using the RADLIG and LIGAND programs (Biosoft, Ferguson, MO) (22).

Flow cytometric analysis

Single cell suspensions of epithelial cells obtained after trypsinization were cultured in petri dishes with constant rocking at 37°C in 5% CO_2 for 24 h to allow reexpression of receptors lost during the treatment with trypsin. The cell number and viability were determined by trypan blue dye exclusion. Approximately 1×10^5 cells were incubated in PBS without divalent cations containing varying amounts of biotinylated mIgA or AIgA (1–10 μg) on ice for 1 h. After washing with PBS-BSA buffer (PBS containing 0.1% BSA and 0.05% NaN_3), cells were incubated with streptavidin-FITC (3 μg/ml) on ice for 1 h. The cells were then washed once quickly and fixed in 1% paraformaldehyde, and 10,000 cells per condition were analyzed for fluorescence by single-color flow cytometry on a FACScan (Becton Dickinson, San Jose, CA). In competition experiments, nonbiotinylated mIgA or AIgA were added for 1 h before addition of the biotinylated IgA. In other experiments, unlabeled mIgA1 were incubated with HT-29 cells as described above, followed by FITC-conjugated anti-IgA Ab (Sigma) and analyzed by single-color flow cytometry. To determine the expression of CD89, intestinal epithelial cells were incubated with a mAb to CD89 (My43) (kindly provided by Dr. Lee Shen, Dartmouth University), followed by FITC-labeled goat anti-mouse IgG (H+L) (Accurate Chemicals, Westbury, NY). PMA-stimulated U937 cells were employed as positive control in this experiment.

RT-PCR for FcαR (CD89) mRNA

Total RNA was extracted from HT-29/19A and T84 intestinal cells and from U937 by the guanidium thiocyanate method with RNAzol B (Life Technologies) and RT-PCR for FcαR was performed with Gene RNA PCR kit components (Perkin-Elmer Cetus, Branchburg, NJ), as previously described (22). First-strand cDNA was synthesized using murine leukemia virus reverse transcriptase and oligo(dT) at 42°C for 60 min. cDNA was amplified using the following primers based on the sequence data for U937 FcαR cDNA (26): 5′-AAGCTTACCTGACCCAGCTGATG-3′ (sense strand) and 5′-AAGCTTCTTAGTGAGCTTTTCTCTC-3′ (antisense strand). The anticipated product contains 701 bases of the translated region and 96 bases of the untranslated 3′ region of FcαR cDNA, for a predicted size of 797 bp. PCR was performed in a DNA thermal cycler (Perkin-Elmer Cetus) programmed as follows: denaturation cycle at 94°C for 15 s, annealing at 58°C for 30 s, and extension at 72°C for 3 min, for a total of 35 cycles. PCR products were resolved alongside pUC18HaeIII DNA marker (Sigma) on a 2% agarose gel containing ethidium bromide, and visualized and photographed under UV light.

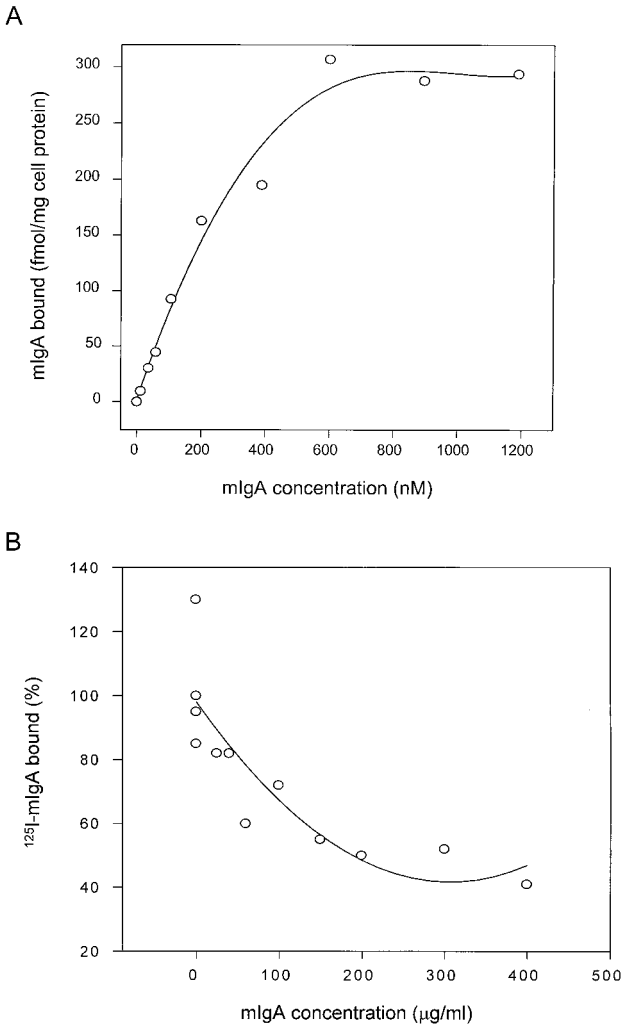

FIGURE 1. *A*, Equilibrium binding of ^{125}I-mIgA to HT-29/19A cells. HT-29/19A cells were incubated for 60 min at 4°C with ^{125}I-mIgA (2 μg/ml) alone or in the presence of increasing concentration of nonradiolabeled mIgA. Results are shown as specific binding (total binding − nonspecific binding). *B*, Specificity of ^{125}I-mIgA binding to HT-29/19A cells. Up to 400 μg/ml of nonradiolabeled mIgA (~200-fold molar excess over the radiolabeled-IgA) displayed maximal inhibition (50–60%) of labeled mIgA binding.

Results

Binding of ^{125}I-mIgA to HT-29/19A cells

Equilibrium binding studies were performed to determine whether mIgA binds to HT-29/19A and to characterize the binding. Fig. 1*A* shows the specific (inhibitable by a large excess of unlabeled IgA) binding of IgA. mIgA bound to HT-29/19A in a dose-dependent manner and was saturable at ~800 nM of mIgA.

To determine the proportion of IgA binding that was specific, increasing concentration of nonradiolabeled mIgA was added to HT-29/19A cells before addition of radiolabeled mIgA. The results of these experiments indicated that mIgA blocked the binding of radiolabeled mIgA in a dose-dependent manner. As shown in Fig. 1*B*, 200–400 μg/ml of nonradiolabeled mIgA (~100-fold molar excess over the radiolabeled-IgA) displayed maximal inhibition (50–60%) of labeled mIgA binding. Quantitation of mIgA binding to HT-29/19A cells (Fig. 2) was performed according to the method of Scatchard (27). The first-order linear regression fit for the Scatchard plot suggested there was a single population of IgA receptors. There were 2.1×10^5 binding sites per cell with an

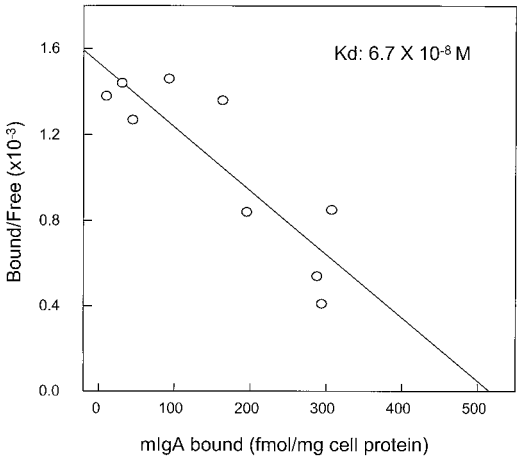

FIGURE 2. Scatchard plot. mIgA binds to HT-29/19A cells with a K_d of 6.7×10^{-8} M. Results are expressed as the mean of four experiments.

affinity constant (K_a) for mIgA of 1.5×10^7 M^{-1}, corresponding to a dissociation constant (K_d) of 6.7×10^{-8} M.

Inhibition experiments with various classes of Igs

The isotype specificity of IgA binding was investigated by determining the pattern of inhibition obtained with various classes of Igs. Cells were incubated with human IgG (50–300 μg/ml) or IgM (50–300 μg/ml) before the addition of ^{125}I-mIgA. Neither IgG nor IgM blocked the mIgA binding (Fig. 3). These data suggest that the binding of IgA was Ig class specific and was not mediated by the pIgR, which binds polymeric forms of IgA and IgM.

Binding of different molecular forms of IgA

To determine the relative binding affinity of different molecular forms of IgA, HT-29/19A cells were first incubated with mIgA, S-IgA or AIgA. Next ^{125}I-mIgA was added. The results shown in Fig. 4 indicate that IgA binding is independent on the molecular size of the IgA, but that S-IgA does not bind to the HT-29/19A cells.

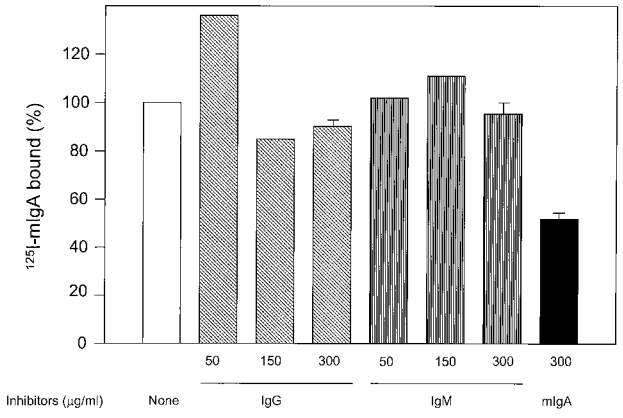

FIGURE 3. Ig isotype specificity of ^{125}I-mIgA binding to HT-29/19A cells. HT-29/19A cells were incubated with ^{125}I-mIgA (2 μg/ml) alone (None), or in the presence of different concentrations of unlabeled human IgG, IgM, and mIgA. Results are presented as the percent of ^{125}I-mIgA bound to the cells in the absence of inhibitors (100% binding). The results are from single experiments for the lowest concentrations of inhibitors. The mean ± SD from three to seven experiments are presented for the highest concentrations.

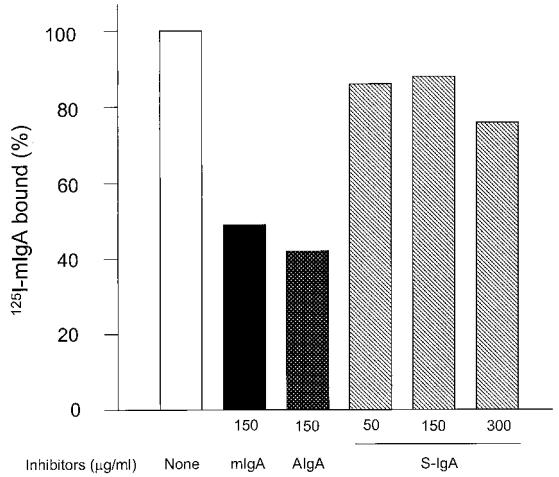

FIGURE 4. Binding of various molecular forms of IgA to HT-29/19A cells. Cells were incubated with ^{125}I-mIgA (2 μg/ml) alone (None), or in the presence of different concentrations of unlabeled mIgA, AIgA, and S-IgA. Results are presented as the percent of ^{125}I-mIgA bound to the cells in the absence of inhibitors (100% binding) or in the presence of unlabeled mIgA, AIgA, and S-IgA .

Inhibition by asialoorosomucoid

Because IgA can bind to the ASGPR (16), which was recently shown to be expressed on HT-29 cells (17), competition experiments were performed using asialoorosomucoid as a potential inhibitor of mIgA binding (28) (Fig. 5). The results indicate that the binding of mIgA to HT-29/19A cells was not mediated by an ASGPR.

Distribution of mIgA binding to intestinal epithelial cells

To confirm by an independent method the binding of mIgA to HT-29/19A cells and to evaluate the proportion of cells that bind mIgA, flow cytometry was performed using biotinylated mIgA as the probe. In these experiments, a dose-dependent binding of IgA to a subpopulation of the HT-29/19A cells (~30% of total cells) was observed (Fig. 6). To demonstrate that this binding was specific, unlabeled mIgA was used to compete for binding of the

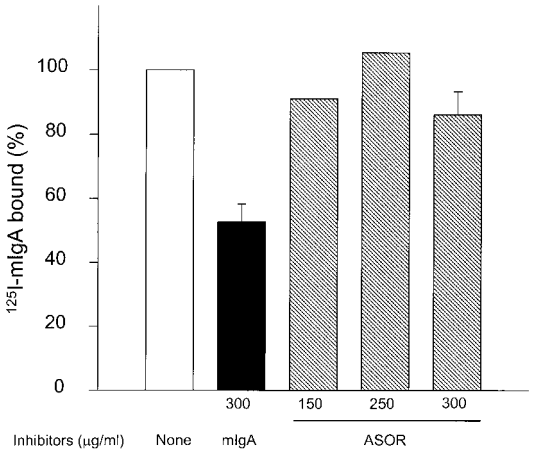

FIGURE 5. mIgA does not bind the ASGPR on HT-29/19A cells. Cells were incubated with ^{125}I-mIgA (2 μg/ml) alone (None) or in the presence of unlabeled mIgA (300 μg), or different concentrations of asialoorosomucoid (ASOR). Results are presented as the percent of ^{125}I-mIgA bound to the cells in the absence of inhibitors (100% binding) (n = 1–7 experiments).

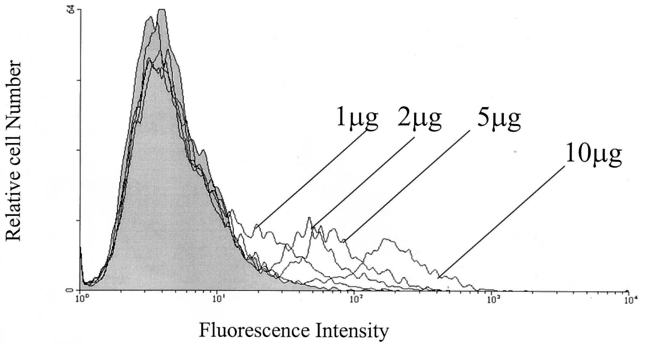

FIGURE 6. Dose-dependent binding of biotinylated-mIgA to a subset of HT-29/19A cells. Cells were incubated with different amounts of biotinylated-mIgA (1–10 μg) followed by streptavidin-FITC. The histogram shows overlays of logarithmic mean fluorescence frequency distribution of 10,000 cells. Cells incubated without IgA, followed by streptavidin-FITC, served as negative control (filled area). A representative experiment from five performed is shown.

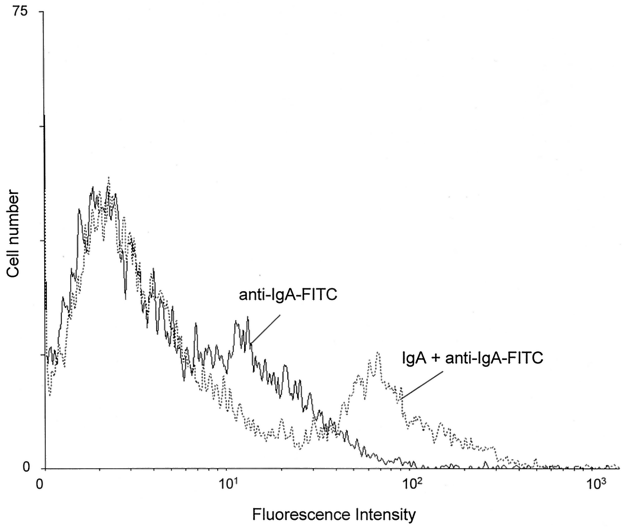

FIGURE 8. Binding of mIgA1 to HT-29 cells. Unlabeled, Jacalin-purified, mIgA1 (5 μg) were incubated with HT-29/19A cells followed by FITC-conjugated anti-IgA Ab. Cells incubated with FITC-conjugated anti-IgA Ab alone served as negative control. The figure is an overlay of two histograms showing the logarithmic fluorescence intensity of 10,000 cells each. A representative experiment from four performed is shown.

biotinylated mIgA. In the presence of 100-fold molar excess of nonbiotinylated mIgA, we observed a reduction in fluorescence intensity to the levels seen for cells incubated without mIgA (i.e., stained only with avidin-FITC) (Fig. 7).

To confirm that binding of biotinylated mIgA to colonic epithelial cells was IgA specific (i.e., not due to other substances copurified by Jacalin affinity chromatography), unlabeled mIgA1 were incubated with HT-29/19A cells, followed by FITC-conjugated anti-IgA Ab. The results of these experiments confirmed that the binding observed with the biotinylated, Jacalin-purified material was indeed due to IgA (Fig. 8). Using the same approach, we could demonstrate that, similarly to mIgA1, mIgA2 also binds to HT-29/19A cells (data not shown).

Flow cytometry studies were also employed to determine whether IgA-binding was a unique characteristic of the HT-29/19A cell line. Therefore, binding of biotinylated mIgA was investigated in T84 and Caco 2 colonic cell lines. Although the distribution pattern differed from that observed in HT-29/19A cells, mIgA binding was nevertheless consistently detected on all of the colonic cell lines tested (Fig. 9).

CD89 expression by intestinal epithelial cells

To exclude the possibility that mIgA binding to HT-29/19A cells was due to the expression of FcαR1 (CD89), steady-state levels of mRNA for CD89 were analyzed by RT-PCR in HT-29, HT-29/19A, and T84 cells. U937 cells were used as positive control. As expected, PMA-stimulated U937 cells expressed CD89 mRNA (Fig. 10*A*). In contrast, HT-29, HT-29/19A, and T84 cells did not express mRNA for CD89. Expression of the housekeeping gene β-actin demonstrated that the RNA from all the cells was intact and that relatively equal amounts of the RT-PCR mixtures were loaded on the gel. To confirm that long-lived FcαR1 protein was not present on the surface of the epithelial cells, we used flow cytometry to examine the binding of My43, a monoclonal IgM Ab to FcαR1, to HT-29/19A and U937 cells. Although a uniform staining was evident for U937 cells, no binding of My43 was detected on HT-29/19A cells (Fig. 10*B*). Thus, these data suggest that

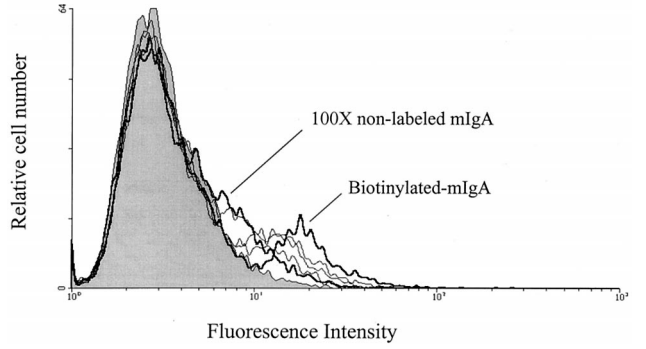

FIGURE 7. Competition for biotinylated-mIgA binding to HT-29/19A cells by unconjugated IgA. Cells were incubated with 100-fold excess of nonbiotinylated mIgA for 90 min before adding biotinylated mIgA (2 μg/ml). The figure shows overlays of two histograms showing logarithmic fluorescence intensity of 10,000 cells each. A representative experiment from five performed is shown.

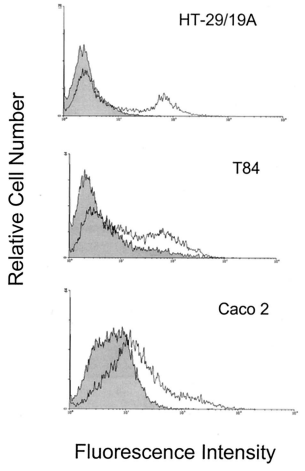

FIGURE 9. mIgA binding to intestinal cell lines. HT-29/19A, T84, and Caco 2 cells were incubated with biotinylated mIgA (10 μg) followed by streptavidin-FITC (open area). Cells incubated without IgA, followed by streptavidin-FITC served as negative control (filled area). The histogram shows overlays of logarithmic fluorescence intensity of 10,000 cells. A representative experiment from three performed is shown.

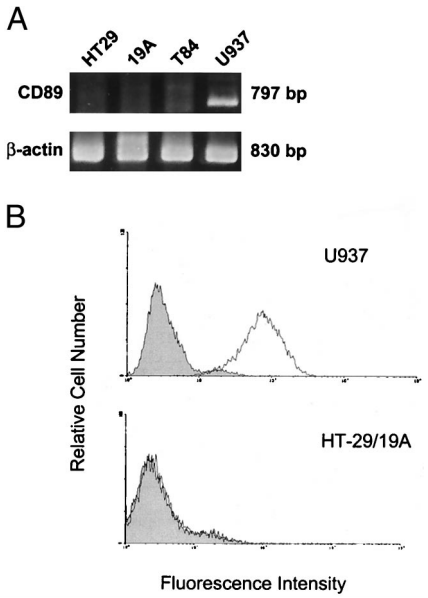

FIGURE 10. Absence of CD89 expression in colon carcinoma cell lines. *A*, Expression of CD89 mRNA by HT-29, HT-29/19A, T84, and by the monocytic cell line U937 was determined by RT-PCR. U937 expresses CD89 mRNA, as previously shown. *B*, CD89 protein on HT-29/19A and U937 was examined by flow cytometry using the mAb My43. As for mRNA, only U937 expresses CD89 protein.

the binding of IgA1 to intestinal epithelial cells was not mediated by the FcαR1.

Discussion

We report in this paper evidence for a novel low-affinity IgA receptor on intestinal epithelial cells. Given the high levels of IgA production in close proximity to the intestinal enterocytes, these receptors may be important in the normal physiology and in pathologic conditions of the gastrointestinal tract. A number of different cell types have been previously shown to bind IgA, but only one receptor, specific for IgA, has been cloned. The expression of FcαR (CD89) seems to be largely restricted to cells of the myeloid lineage (5–15), and perhaps to mesangial cells under certain circumstances (21). However, we have recently shown that cultured (passages three to six) human mesangial cells do not express CD89, but bind IgA with an affinity lower than that described for myeloid cells (22). Interestingly, these mesangial cells bound monomeric and aggregated IgA with similar affinity, but did not bind S-IgA (our unpublished results).

Experiments presented herein indicate that colonic epithelial cells also have receptors which specifically bind IgA. Again, the presence of secretory component (and/or J chain) on S-IgA seems to prevent their binding to this receptor. These characteristics appear to distinguish the epithelial receptor from all other IgA receptors described previously. Because our experiments were performed in PBS without divalent cations, the binding of mIgA to HT-29/19A cells observed in our study was not mediated by β1-4 galactosyltransferase (18). We also performed additional experiments that excluded the possibility that the mIgA binding we observed in the colonic cell lines was due to the previously described FcαR or the ASGPR. Further, the use of mIgA as the primary ligand and the lack of inhibition by IgM suggest that the pIgR, known to be present on HT-29/19A cells (23), is not responsible for the IgA binding we observed on colonic cells. Finally, the lack of binding of S-IgA distinguishes the receptor on HT-29/19A from that described on eosinophils, which only binds S-IgA and free secretory component (29, 30). The IgA receptors that have been described on B lymphocytes, T lymphocytes, and NK cells have not been fully characterized and thus cannot be distinguished from those we have described on mesangial and epithelial cells. A summary of the characteristics that differentiate the epithelial cell IgA receptors described here from those described previously is shown in the Table I.

The Ig receptors can be classified based on their structures and/or functions (31). Because we have not yet isolated or cloned the epithelial receptor, its structure remains unknown. Based on the binding characteristics, the receptor on the surface of the epithelial cell would become saturated with IgA Abs when the local IgA concentration exceeds about 100 μg/ml. This concentration of IgA is present in many secretions (32) and might be achieved at the basolateral surfaces of the enterocyte. However, as in the case of low affinity Fc receptors, the epithelial IgA receptor could also bind a pre-formed complex containing IgA. Binding such complexes is often associated with signaling events, which lead to cellular activation. Indeed, in mesangial cells that lack FcαR but bind IgA, we found that addition of AIgA, but not mIgA, induced a cellular signal, as indicated by enhanced expression of the immediate early gene, c-Jun (22). We are currently seeking evidence for such an activation process after IgA binds to epithelial cells.

Binding to some Ig receptors can result in internalization and transcellular transport of intact Igs, as in the case of the pIgR (33) and Fcγn receptor of the neonatal rodent (34). The outcome of these processes is epithelial secretion or intestinal or transplacental uptake of Igs, respectively. Similarly, the ASGPR mediates internalization of glycoproteins, including Ig, but the major outcome is intracellular degradation of the ligand and recycling of the receptor

Table I. *Characteristics of IgA receptors*

	Ligands	Cell Types Expressing	Distinguishing Characteristics of Epithelial Receptor	Ref.
New epithelial receptor	Serum IgA1, IgA2, and aggregated IgA	Epithelial cells		This study
Mesangial cell receptor	Serum IgA1, and aggregated IgA	Mesangial cells	Not known	22
β-Galactosyltransferase	Polymeric IgA, mIgA1/A2, S-IgA	Liver, myeloid, epithelial cells	Cation-independent binding	18
FcαR (CD89)	IgA1, IgA2, S-IgA	Myeloid cells	No mRNA by RT-PCR; no staining with My43	5–15
pIgR	Polymeric IgA, IgM	Secretory epithelial cells	Binds mIgA; no inhibition by IgM	Reviewed in 4
ASGPR	Terminal galactose and *N*-acetyl galactosamine	Liver, myeloid epithelial cells	No inhibition by asialoorosomucoid	16, 17
S-IgAR	S-IgA/free SC	Eosinophils, basophils	Binds serum IgA, not S-IgA	29, 30

to the cell surface (34). We have not explored in detail the possibility that the colonic epithelial or mesangial IgA receptor mediates such a process, but preliminary results suggest that neither cell specifically internalizes or degrades the IgA which binds to their cell surface receptors (results not shown).

Thus, we do not yet know either the structure or function of the IgA-specific receptor on intestinal epithelial cells, nor do we know the cell surface localization. However, based on the similarities between the mesangial cell and epithelial cell IgA receptors, we are currently investigating the effect of IgA on intracellular signaling pathways that are associated with the transcriptional activation of inflammatory genes in epithelial cells. The potential adaptive response of epithelial cells to such signals and the pathologic consequences of persistent activation may be important areas for future investigations.

Acknowledgments

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