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Immunology

The polymeric immunoglobulin receptor (secretory component) mediates transport of immune complexes across epithelial cells: A local defense function for IgA

(epithelial transcytosis/mucosal immunity)

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ABSTRACT **The polymeric immunoglobulin receptor (pIgR) on mucosal epithelial cells binds dimeric IgA (dIgA) on the basolateral surface and mediates transport of dIgA to the apical surface. Using Madin–Darby canine kidney epithelial cells stably transfected with pIgR cDNA, we found that soluble immune complexes (ICs) of ^{125}I-labeled rat monoclonal anti-dinitrophenyl (DNP) dIgA (^{125}I-dIgA) and DNP/biotin–bovine serum albumin were transported from the basolateral to the apical surface and then released. Monomeric IgA ICs were not transported, consistent with the specificity of pIgR for polymeric immunoglobulins. Essentially all the ^{125}I-dIgA in apical culture supernatants was streptavidin precipitable, indicating that dIgA remained bound to antigen during transcytosis. While both dIgA and dIgA ICs bound pIgR with equal affinity ($K_d \approx 8$ nM), the number of high-affinity binding sites per cell was 2- to 3-fold greater for dIgA than for dIgA ICs. The extent of endocytosis of dIgA and dIgA ICs was correlated with the number of high-affinity binding sites. SDS/PAGE analysis of intracellular dIgA and dIgA ICs demonstrated that in both cases IgA remained undegraded during transport. The results suggest that the pathways of epithelial transcytosis of free dIgA and dIgA ICs are the same. Given the high population density of mucosal IgA plasma cells and the enormous surface area of pIgR-expressing mucosal epithelium, it is likely that significant local transcytosis of IgA ICs occurs *in vivo*. Such a process would allow direct elimination of IgA ICs at the mucosal sites where they are likely to form, thus providing an important defense function for IgA.**

Secretory IgA is the first line of immune defense, interacting with a variety of environmental antigens (1–4). Traditionally this form of IgA has been viewed as an immunological barrier designed to combine with antigens external to body tissues, as in the lumen of the intestinal or respiratory tracts, and prevent foreign matter from impinging on the lining epithelium and entering the body proper. However, immune complexes (ICs) containing IgA may also form within the mucous membranes if foreign macromolecules should penetrate the epithelium or if infectious agents are replicating locally. In such cases, IgA ICs could gain access to the systemic circulation and deposit in tissues or organs such as the spleen, liver, or kidney (5). On the other hand, direct elimination of IgA ICs at the mucosal sites where they are likely to form could minimize negative pathophysiological consequences of IC deposition within body tissues systemically and could provide an important, but hitherto unappreciated, defense mechanism.

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The transport of secretory IgA into external fluids is mediated by the polymeric immunoglobulin receptor (pIgR), expressed on the basolateral surface of mucosal epithelial cells (6–11). The complex of pIgR and dimeric IgA (dIgA) is endocytosed and transported through vesicular compartments to the apical surface, where proteolysis of pIgR between the ectoplasmic and membrane-spanning domains results in release of dIgA bound to the ectoplasmic domain of pIgR (also known as secretory component). Mostov and Deitcher (12) have developed a model for studying epithelial transcytosis of IgA by using Madin–Darby canine kidney (MDCK) cells stably transfected with rabbit pIgR cDNA. Here we demonstrate that MDCK cells expressing pIgR vectorially transport dimeric IgA ICs and that antigen remains bound to the dIgA throughout transcytosis. Accordingly, we suggest that transport of IgA ICs by mucosal epithelial cells could be an important and efficient mechanism for ridding the body of ICs directly at sites of their formation, thereby excluding antigen and ICs from the systemic circulation.

MATERIALS AND METHODS

Cell Culture. Wild-type strain II MDCK cells and MDCK cells stably transfected with cDNA for rabbit pIgR (pWE cells from Keith Mostov, University of California, San Francisco) (12) were cultured in minimal essential medium (MEM) with nonessential amino acids and Earle's salts (Sigma) with 10% (vol/vol) fetal calf serum.

Preparation of IgA ICs. Monomeric IgA (mIgA) and polymeric IgA were isolated as described from ascitic fluid of rats injected with IR 1060 cells, a rat hybridoma secreting monoclonal IgA with specificity for dinitrophenyl (DNP) (13). Dimeric IgA was separated from higher polymers by gel filtration, and purity of the monomeric (mIgA) and dimeric (dIgA) fractions was confirmed by SDS/PAGE (14). IgA was labeled with ^{125}I to a specific activity of $1.0–1.5 \times 10^8$ cpm/μg via lactoperoxidase (15). DNP was conjugated to bovine serum albumin (BSA) as described (16); the molar ratio of DNP/BSA was calculated to be 3.5:1, based on the ratio of absorbance at 360–280 nm (16). For some experiments, biotin was covalently coupled to DNP–BSA via biotin–*N*-hydroxysuccinimide ester (BRL) (17). ICs were prepared by incubating ^{125}I-labeled mIgA (^{125}I-mIgA) or ^{125}I-dIgA at 37°C for 30 min and then at 4°C for 16 hr, with an antigen

Abbreviations: dIgA, dimeric IgA; mIgA, monomeric IgA; IC, immune complex; MDCK, Madin–Darby canine kidney; DNP, dinitrophenyl; BSA, bovine serum albumin; TCA, trichloroacetic acid; pIgR, polymeric immunoglobulin receptor.

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concentration determined by quantitative immunoprecipitation to be 12 times equivalence. In some experiments, dIgA was incubated with DNP-glycine to block the antigen-binding sites. Final concentrations were 1 μg of mIgA or dIgA and 10.2 μg of DNP–BSA or 10.2 μg of DNP/biotin–BSA, or 0.035 μg of DNP-glycine per ml of Hepes buffer [0.05 M Hepes, pH 7.4/0.118 M NaCl/0.005 M KCl/0.0012 M $MgSO_4$/0.01 M $CaCl_2$/0.0088 M glucose/1% (wt/vol) BSA, which was treated at 56°C for 30 min to inactivate endogenous proteases]. Insoluble ICs were removed by centrifugation (12,000 × *g*; 10 min). The average size of the ICs was determined by gel filtration on a 1.5 × 30 cm column of Sepharose 4B (Pharmacia) in PBS.

Transcytosis of IgA and IgA ICs. MDCK cells or pWE cells were grown to confluence on 30-mm nitrocellulose filter chambers (Millicell-HA; Millipore). The integrity of each monolayer was tested by measuring transmembrane electrical resistance with a Millicell-ERS meter (Millipore), typically 150–375 Ω·cm^2. Filters were rinsed at 0°C with Dulbecco's PBS (10 mM Na_2HPO_4, pH 7.4/150 mM NaCl/4.1 mM KCl/0.5 mM $CaCl_2$/0.9 mM $MgCl_2$), 1.0 ml of Hepes buffer was added to the upper (apical) chamber, and the filters were placed in 35-mm culture dishes containing 1.5 μg of ^{125}I-mIgA, ^{125}I-dIgA, ^{125}I-mIgA IC, or ^{125}I-dIgA IC in 1.5 ml of Hepes buffer. Filters were incubated at 0°C for 3 hr to allow binding of IgA or IgA ICs to the basolateral surface of the monolayer. Unbound IgA or IgA ICs were removed by rinsing the filters with ice-cold Dulbecco's PBS containing 0.1% BSA. The cell monolayers were then rapidly warmed by adding 37°C Hepes buffer (without BSA) to the apical and basolateral surfaces of the filters and placing in a 37°C incubator. In experiments that were carried out for 24 hr, complete MEM was used in place of Hepes buffer. Samples of apical medium were collected at various time points after filters were warmed to 37°C.

To determine total IgA transported, 200-μl aliquots of apical medium were precipitated with 10% trichloroacetic acid (TCA). To determine the fraction of transported IgA bound to antigen (DNP/biotin–BSA), 200-μl aliquots of apical medium were precipitated with streptavidin/agarose (BRL). To control for nonspecific binding to agarose, duplicate 200-μl aliquots of apical medium were precipitated with an equivalent volume of Sepharose 4B (Pharmacia).

Measurement of Binding Affinity of dIgA and dIgA ICs for pWE Cells. pWE cells cultured on plastic dishes were detached with 0.2% (wt/vol) EDTA in Hanks' balanced salt solution (HBSS) without Ca^{2+} or Mg^{2+} and added to a concentration of 10^6 cells per 0.75 ml with 5×10^{-13} mol of ^{125}I-dIgA or ^{125}I-dIgA ICs and various concentrations of unlabeled dIgA or dIgA ICs in Hepes buffer. Cells were incubated at 0°C for 3 hr, collected by centrifugation (500 × *g*; 10 min), and then washed four times with Dulbecco's PBS. Cell-associated radioactivity was determined, mol of bound dIgA or dIgA ICs was calculated, and equilibrium dissociation constants (K_d) and number of binding sites per cell were determined by Scatchard analysis (18).

Endocytosis of dIgA and dIgA ICs. pWE cells were grown on nitrocellulose filters, and binding of ^{125}I-dIgA or ^{125}I-dIgA ICs was carried out as described above except that the antigen was DNP–BSA without conjugated biotin. Filters were warmed to 37°C for various intervals to allow for endocytosis of dIgA or dIgA ICs and then chilled to prevent further internalization. To remove cell surface-bound dIgA or dIgA ICs, apical and basolateral surfaces of filters were incubated for 1 hr at 0°C with Pronase at 2 mg/ml (Calbiochem) and 0.4% EDTA in HBSS without Ca^{2+} or Mg^{2+}. Filters were rinsed with ice-cold Dulbecco's PBS with 0.05% NaN_3 and 0.1% BSA. Cells were then gently scraped off the filters into 1 ml of Dulbecco's PBS, washed, and collected by centrifugation as before. Cell pellets were lysed in 0.1 M Na_2HPO_4/1.0% (vol/vol) Triton X-100/5 mM EDTA/100 kallikrein inhibitor units of aprotinin per ml (Sigma)/0.5 mM soybean trypsin inhibitor (Sigma)/0.5 mM phenylmethylsulfonyl fluoride (Sigma). Cell lysates were cleared of denatured DNA and protein as described (19). To determine the concentration of intracellular ^{125}I-dIgA or ^{125}I-dIgA ICs, 75-μl aliquots of the clarified supernatants were precipitated with TCA. The effectiveness of the Pronase treatment in removing cell-surface dIgA or dIgA ICs was confirmed by the observation that Pronase removed all the ^{125}I from cells that were maintained at 0°C (thus preventing endocytosis) prior to Pronase digestion (see Fig. 4). To determine the extent of degradation of intracellular ^{125}I-dIgA or ^{125}I-dIgA ICs, aliquots of clarified supernatant containing 4000 cpm were analyzed by reducing SDS/PAGE in a 5% stacking/10% separating acrylamide gel (14). Gels were dried and exposed to Kodak XAR-5 film. The lack of degradation of intracellular dIgA or dIgA ICs (see Fig. 5) demonstrated that prior Pronase treatment of the cells affected only cell-surface proteins.

RESULTS

dIgA and dIgA ICs, but Not mIgA or mIgA ICs, Are Vectorially Transported Across pWE Cells. To test the ligand specificity of IgA transcytosis, ^{125}I-mIgA, -dIgA, -mIgA ICs, or -dIgA ICs were added to the basolateral surface of MDCK cells expressing rabbit pIgR (pWE cells), and transcytosis was determined by sampling the apical medium at various intervals. While the time course of transport was indistinguishable for dIgA and dIgA ICs, the magnitude of dIgA transport was consistently 6- to 8-fold higher for free dIgA than for dIgA ICs (Fig. 1). Transport of both ligands was mediated by pIgR since no transport was observed in polarized monolayers of MDCK cells not transfected with pIgR (data not shown). In contrast to dIgA and dIgA ICs, neither mIgA nor mIgA ICs were transported, consistent with the specificity of pIgR for polymeric immunoglobulins. The observation that mIgA ICs were not transported indicates

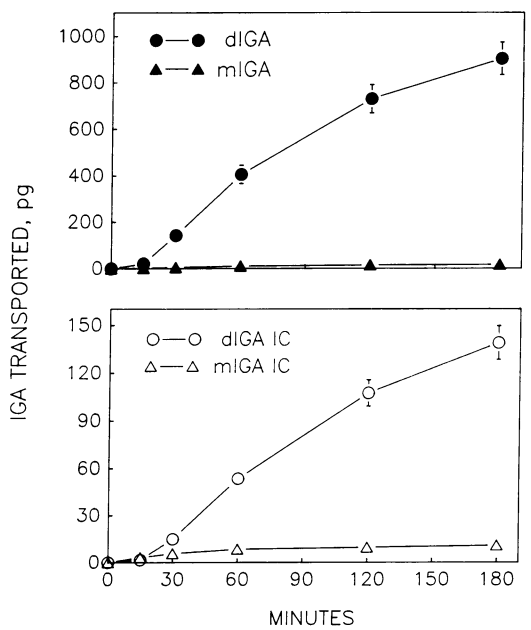

FIG. 1. Transcytosis of IgA and IgA ICs. ^{125}I-mIgA or -dIgA (*Upper*), or ^{125}I-mIgA or -dIgA ICs (*Lower*) were allowed to bind at 0°C to the basolateral surface of pWE cell monolayers. Cultures were warmed to 37°C for various intervals, and transcytosed IgA or IgA ICs were detected by measuring TCA-precipitable ^{125}I in the apical culture supernatants. This experiment was repeated three times; data from a representative experiment are expressed as means ± SD (n = 3).

that pIgR does not recognize multiple monomer IgA molecules cross-linked by antigen and suggests that its ligand specificity requires either the presence of J chain (found in dIgA but not in mIgA) or the particular conformation of polymeric immunoglobulins.

Antigen Remains Bound to dIgA During Transcytosis. To determine whether transported dIgA antibody remained bound to antigen, apical culture supernatants were precipitated with streptavidin/agarose to selectively detect complexes of ^{125}I-dIgA bound to DNP/biotin–BSA. Between 80% and 95% of the dIgA in apical medium from cultures incubated with dIgA ICs was streptavidin precipitable, exactly the same proportion as was observed for the dIgA IC starting material (data not shown). In contrast, <10% of the dIgA in apical medium from cultures incubated with dIgA alone was streptavidin precipitable. In control experiments, we demonstrated that ^{125}I-labeled DNP/biotin–BSA was not transported across pWE cells in the absence of dIgA antibody, ruling out the possibility that dIgA and antigen were transcytosed separately and became complexed after release into the apical medium. Taken together, these data suggest that dIgA ICs remain intact during epithelial transcytosis.

The pIgR on pWE Cells Binds dIgA and dIgA ICs with Equal Affinity. To analyze structural differences between dIgA and dIgA ICs that might give rise to quantitative differences in transport, the relative sizes of ^{125}I-dIgA and ^{125}I-dIgA ICs were compared by gel filtration (Fig. 2). The elution of dIgA was consistent with its expected molecular mass of 325 kDa. The relatively uniform size of 900–1000 kDa for dIgA ICs was consistent with a structure composed of two 325-kDa dIgA molecules complexed with five or six 68-kDa DNP–BSA molecules. Given the 1:1 stoichiometry of free dIgA binding to pIgR, we predicted that two binding sites for pIgR could be present on each dIgA IC, unless steric factors prevented the simultaneous binding of both dIgA molecules. Since no peak of ^{125}I-labeled material in the dIgA IC preparation was seen eluting at the size for dIgA, we can conclude that the observed transport of dIgA ICs did not reflect the transport of a small population of free dIgA molecules present in the dIgA IC preparation, a conclusion that is further supported by the observation that antigen remained bound to dIgA during transcytosis.

To compare the behavior of the two ligands at individual stages of the transport pathway, we first analyzed the binding of dIgA and dIgA ICs to the surface of pWE cells by Scatchard analysis (Fig. 3 and Table 1). High-affinity binding sites, with K_d values on the order of 6–9 nM, were observed for both dIgA and dIgA ICs. Because of the experimental conditions of the binding assay, the measured K_d values could differ somewhat from the absolute values. Nevertheless, they do reflect the relative ability of dIgA and dIgA ICs to bind pIgR. Moreover, the observed dissociation constants were on the same order as those reported for rabbit dimeric IgA binding to pIgR on isolated rabbit mammary cells, mammary cell membranes, and liver cell membranes (20, 21). Since transcytosis of both dIgA and dIgA ICs required expression of pIgR and since neither free mIgA nor cross-linked mIgA ICs were transported, we believe that the high-affinity binding site, which is shared by both ligands, is indeed pIgR. The number of high-affinity binding sites per cell was ≈2-fold greater for dIgA than for dIgA ICs, suggesting that steric factors may have lowered the effective density of binding sites for dIgA ICs. A second class of higher-abundance, lower-affinity binding sites (K_d 19 nM) was consistently observed for dIgA but not for dIgA ICs. Adding the high- and low-affinity binding sites, we observed a total binding capacity for dIgA that was ≈6-fold higher than for dIgA ICs. Significantly, this difference in binding capacity was on the same order as the observed quantitative difference in transport of dIgA and dIgA ICs (Fig. 1), suggesting that increased transport of dIgA may have resulted simply from the presence of a larger pool of ligand bound to the cell surface. Since a major structural difference between dIgA and dIgA ICs is the presence of antigen, we considered the possibility that some of the free dIgA may have interacted by way of its antigen-combining site with a cross-reactive epitope on the surface of pWE cells. To test this possibility, we preincubated free ^{125}I-dIgA with a 50-fold molar excess of DNP-glycine to block the antigen-combining sites without cross-linking the dIgA molecules. However, transcytosis of dIgA bound to DNP-glycine was indistinguishable from free dIgA (data not shown), suggesting that free dIgA did not bind to an epitope on pWE cells that cross-reacted with DNP. While the nature of the lower-affinity binding site for dIgA remains unknown, we hypothesize that this cell-surface structure may have acted as a binding reservoir for dIgA once the high-affinity sites had been saturated.

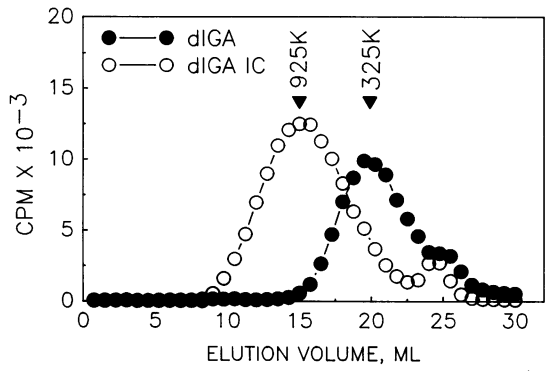

FIG. 2. Gel filtration of dIgA and dIgA ICs. ^{125}I-dIgA and -dIgA ICs were separately analyzed by passage through a column of Sepharose 4B in PBS, and cpm in 0.5-ml fractions was measured. Molecular size markers: 925 kDa, IgM; 325 kDa, dIgA.

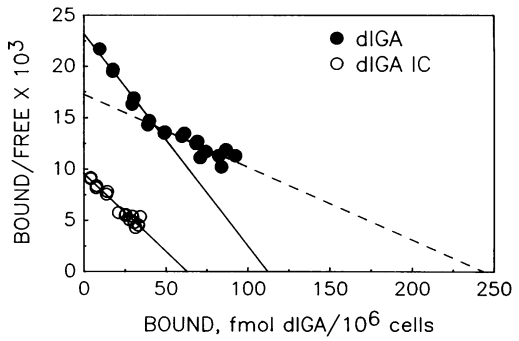

FIG. 3. Scatchard analysis of binding of dIgA and dIgA ICs to pWE cells. ^{125}I-dIgA or -dIgA ICs (5×10^{-15} mol) and various concentrations of unlabeled dIgA or dIgA ICs were incubated with 10^6 pWE cells in 0.75-ml of Hepes buffer. Solid lines, high-affinity binding sites for dIgA or dIgA ICs; dashed line, low-affinity binding site for dIgA. This experiment was repeated four times; individual data from a representative experiment are shown.

Table 1. Scatchard analysis of binding of dIgA and dIgA ICs to pWE cells

Ligand	K_d, nM	Receptors per cell
dIgA	6.4	67,000
	18.8	147,000
dIgA ICs	8.8	38,000

Data from Fig. 3 were analyzed according to Scatchard (18), demonstrating the presence of two classes of binding sites for dIgA and a single class of binding site for dIgA ICs.

Endocytosis of dIgA and dIgA ICs. To examine the relationship between the number of high-affinity binding sites and the rate of endocytosis, we measured the rate of endocytosis of ^{125}I-dIgA and ^{125}I-dIgA ICs by pWE cells over a 24-hr period (Fig. 4). When cultures were warmed to 37°C, endocytosis of both ligands was rapid, initially peaking at 30 min. The magnitude of this initial phase of endocytosis was ≈3-fold higher for dIgA than for dIgA ICs, roughly consistent with the average 2- to 3-fold difference in number of high-affinity binding sites for these two ligands (Table 1 and data not shown from other binding experiments). A second peak in intracellular dIgA was observed at 2 hr, after which time its concentration declined steadily. In contrast, intracellular concentrations of dIgA ICs remained fairly constant or increased slightly for up to 4 hr and then declined slowly for up to 24 hr. After 4 hr, intracellular concentrations of dIgA and dIgA ICs were similar. As observed in previous experiments (cf. Fig. 1), the magnitude of transcytosis of free dIgA was significantly greater than dIgA ICs and continued at a high rate for up to 24 hr (data not shown), suggesting that multiple rounds of internalization and transport of dIgA had occurred. In contrast to the high rate of dIgA transcytosis throughout the experiment, all the dIgA ICs ultimately released into the apical medium could be accounted for by the dIgA ICs that were internalized within the first 4 hr. The apparent occurrence of multiple rounds of dIgA internalization and transport is consistent with the hypothesis that a residual pool of dIgA existed on the cell surface, presumably bound to low-affinity sites, which did not mediate endocytosis. This pool of surface-bound dIgA could be made available to newly expressed pIgR molecules on the cell surface after the first wave of pIgR-mediated endocytosis had occurred. Alternatively, multiple rounds of dIgA internalization could have resulted from recycling of endocytosed dIgA back to the basolateral surface, as previously reported in pWE cells (22). In summary, we conclude that the magnitude of transport of either dIgA or dIgA ICs is determined by local concentrations of these ligands at the cell surface.

Intracellular Degradation of dIgA and dIgA ICs Is Minimal. A difference in intracellular degradation of dIgA and dIgA ICs could suggest that free vs. complexed IgA might be targeted differentially for transport vs. lysosomal degradation and could account for the lesser amounts of dIgA ICs detected in apical culture supernatants. Accordingly, the TCA precipitability of intracellular dIgA and dIgA ICs was compared in cell lysates from the endocytosis experiment described in Fig. 4. The mean TCA precipitability of both dIgA and dIgA ICs was 96% or higher for all time points

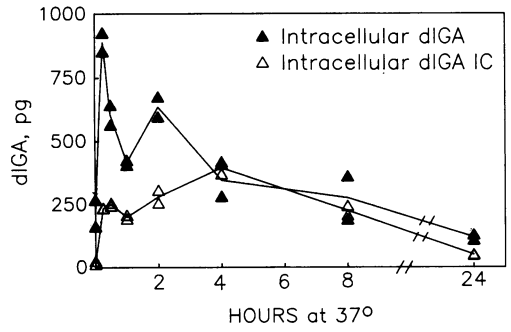

FIG. 4. Endocytosis of dIgA and dIgA ICs. ^{125}I-dIgA or -dIgA ICs were bound at 0°C to the basolateral surface of pWE cells, which were warmed to 37°C for the indicated times and then rapidly chilled to 0°C to prevent further internalization. Cell surface-bound dIgA or dIgA ICs were removed by treatment with Pronase, and internalized dIgA or dIgA ICs were calculated from the radioactivity remaining with the cell pellet. This experiment was repeated four times; individual data from a representative experiment are shown.

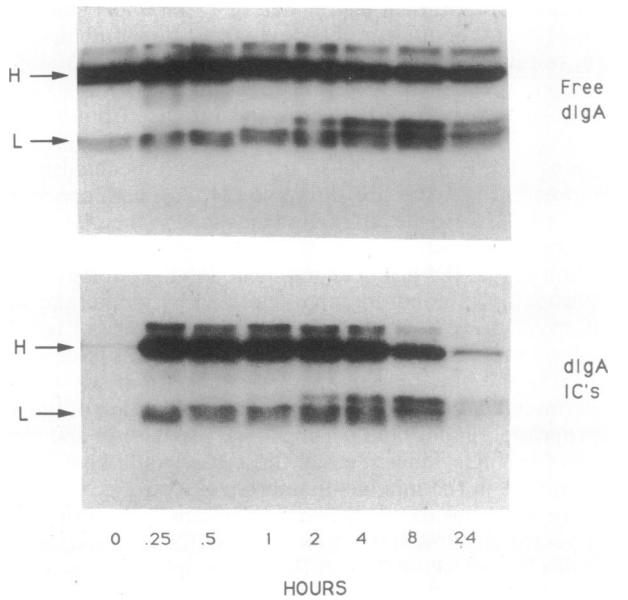

FIG. 5. Intracellular degradation of dIgA and dIgA ICs is minimal. Cell pellets from the experiment described in Fig. 4 were extracted with 1% Triton X-100 and analyzed by SDS/PAGE and autoradiography. To each lane was added 4000 cpm with the exception of the lanes representing the 0- and 24-hr time points for the dIgA ICs, to which were added 350 and 1900 cpm, respectively. Arrows indicate the migration of IgA heavy (H) and light (L) chains in the starting material.

except 24 hr, at which point it was still as high as 93% and 89% for dIgA and dIgA ICs, respectively. For all time points except 24 hr the TCA precipitability of both ligands was greater than that of the starting material, indicating that only intact ligands had bound to the cell surface and had been internalized. To test the possibility that partial intracellular degradation had occurred, resulting in the release of large proteolytic fragments that were still TCA precipitable, cell lysates were also analyzed by SDS/PAGE (Fig. 5). Again, the patterns were indistinguishable for dIgA and dIgA ICs. While there was evidence of partial degradation of heavy chains at 2 hr and beyond (presumably from proteolysis at the hinge region), most of the intracellular free dIgA and dIgA ICs were undegraded. Taken together, the results of the endocytosis and intracellular degradation experiments suggest that the pathways of transcytosis of dIgA and dIgA ICs are essentially the same.

DISCUSSION

The daily production of antibodies of the IgA isotype exceeds that of all other immunoglobulin isotypes combined (2–4) and derives primarily from plasma cells in the lamina propria of mucous membranes. While much of this IgA is directly transported via pIgR into external secretions, significant concentrations of IgA-containing ICs likely form within mucous membranes when antigens are present. Thus, locally synthesized IgA may serve the dual functions of acting as a lumenal barrier to antigen penetration, as well as trapping antigens that penetrate the mucosal epithelium or are synthesized within the mucosa itself as may occur during infections. Although IgA ICs formed in the mucosae might prove harmful if they were to gain access to the systemic circulation, the enormous surface of mucosal epithelium in locations like the intestinal and respiratory tracts provides a vast population of cells that have the potential to eliminate IgA ICs locally.

Previous studies of clearance of IgA ICs have focused mainly on systemic clearance (23–29). Intravenously admin-

istered IgA ICs or heat-aggregated IgA are rapidly cleared by cells of the mononuclear phagocyte (reticuloendothelial) system, primarily by the Kupffer cells in the liver (26, 28). In addition, in rodents a pIgR-mediated pathway allows hepatocellular transport of both IgA and IgA ICs from blood to bile (23, 24, 30), but this pathway is not so important in humans (4, 31, 32). Because the systemic mechanisms for clearance of IgA ICs are saturable (24, 26), high concentrations of IgA ICs in the circulation may lead to their deposition in inappropriate sites, such as the kidney. Indeed, overproduction of IgA ICs has been implicated in the etiology of IgA nephropathy, a condition characterized by glomerular deposition of IgA (27, 28). While systemic clearance of IgA ICs is important in those situations in which IgA ICs have gained access to the blood circulation, the question arises whether experiments involving intravenous administration of IgA ICs appropriately model the usual *in vivo* production and clearance of IgA ICs, since most of these ICs would be expected to originate in the mucous membranes.

Here we demonstrate that epithelial cells expressing pIgR can vectorially transport dimeric IgA ICs and that antigen remains bound to the IgA antibody throughout transcytosis. Mucosal epithelial cells, which constitutively express pIgR, could therefore participate in the clearance of ICs directly at sites of their formation, excluding both antigen and ICs from the systemic circulation. A mechanism of local clearance as the primary means for ridding the body of IgA ICs could also explain why rates of systemic clearance and levels of circulating IgA ICs are poor predictors of IgA IC-induced renal injury (27, 28).

Mucosal clearance of IgA ICs could readily exploit the relatively nonphlogistic character of IgA (1, 5), serving to minimize inflammatory responses to these ICs and reducing the likelihood of negative pathophysiological consequences of their presence. This means of limiting the body's systemic exposure to foreign molecules and circulating ICs could also help prevent immune, including autoimmune, diseases. In the absence of IgA, free foreign molecules or ICs formed by IgG antibodies, which would be more phlogistic than IgA ICs, could gain access to the systemic circulation. This idea is consistent with the well-recognized increased incidence of autoimmunity in the presence of IgA deficiency (33).

We found that endocytosis of IgA ICs as well as IgA was proportional to the number of cell-surface receptors. Accordingly, the enormous number of mucosal epithelial cells expressing pIgR in locations like the respiratory and intestinal tracts (34) should provide the capacity for highly efficient transcytosis of both free IgA and IgA ICs. In addition, during nearby inflammatory or immune responses, up-regulation of pIgR by locally produced cytokines such as interferon γ (35, 36), tumor necrosis factor α (37), and interleukin 4 (36) could further increase the capacity for clearance of IgA ICs in situations in which increased levels of foreign antigens are present within the mucosae.

Collectively, the high population density of mucosal IgA plasma cells, the vast surface area of mucosal epithelium at the interface between the body proper and the external environment, and the ability to up-regulate the epithelial pIgR would make it possible to rid the body nonphlogistically of substantial amounts of ICs. We conclude that in addition to the traditional role of IgA as an immunological lumenal barrier, direct elimination of locally formed intramucosal IgA ICs by mucosal epithelial cells could provide an important defense mechanism mediated by IgA.

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