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*J Immunol* 1998; 161:4340-4346;

http://www.jimmunol.org/content/161/8/4340

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Interaction with Secretory Component Stimulates Effector Functions of Human Eosinophils But Not of Neutrophils

Youichi Motegi and Hirohito Kita

Eosinophils play important roles in the pathophysiology of allergic diseases, such as bronchial asthma and allergic rhinitis, and in host immunity to parasitic infections (reviewed in Ref. 1). During such inflammatory reactions, eosinophils release toxic granule proteins, which act as cytotoxins on a variety of cell types, including tracheal epithelial cells, pneumocytes, and parasites (reviewed in Ref. 1). In humans, eosinophils are tissue-resident cells with >99% residing in tissues, especially in the mucosal tissues (2). In healthy individuals, eosinophils are normally found only in the intestine (2). In specimens from patients with bronchial asthma, eosinophils and released toxic granule proteins are found in the damaged epithelium of bronchial tissues (3–5). In specimens from patients with intestinal parasitic diseases, with allergic gastroenteritis or with celiac disease, eosinophils are detected in large numbers in the lamina propria of the small and large intestines (1). Furthermore, eosinophil infiltration and degranulation are also observed in nasal epithelium of patients with upper respiratory allergy (6) and in biliary tracts of patients with obstructive hepatic diseases (7). Thus, the association between eosinophils and mucosal tissues in both healthy individuals and patients led us to speculate on the specific role(s) of eosinophils in mucosal inflammation and/or immunity.

Secretory IgA (S-IgA)³ is the main Ab secreted by the mucosa of the airways, gastrointestinal tract, and other mucosal tissues (reviewed in Ref. 8). A high proportion of Ig-producing cells in the mucosal lymphoid tissue is committed to the IgA isotype, and the majority of IgA in mucosa is derived from local synthesis (9). Receptors for the Fc portion of IgA (FcγR) have been established on a variety of cell types, including lymphocytes (10, 11), monocytes/macrophages (12, 13), neutrophils (14, 15), and eosinophils (16). The importance of IgA in mucosal immunity is further supported by the presence of secretory component (SC) in S-IgA (17). Epithelial cells express the polymeric Ig receptor, which binds and mediates the transepithelial transport of IgA from the basolateral side of the cells into the lumen (8, 18). The SC is a soluble proteolytic cleavage fragment of the extracellular domain of membrane-bound polymeric Ig receptor (19). Addition of SC to IgA confers increased stability on the resultant S-IgA by helping to hold the IgA monomers together (20) and by masking proteolytic sites from proteases present in mucosal secretions (21); however, the effect of the addition of SC on the biologic activity of IgA is unknown. Recent studies showed that SC did not modify the ability of IgA to mediate hemagglutination inhibition and to neutralize influenza virus in vitro (22).

The SC consists of five Ig-like domains (23); this structure is used commonly as a cell surface receptor and an adhesion molecule. Furthermore, S-IgA immobilized onto Sepharose 4B beads potently stimulates eosinophil degranulation (24). These observations lead us to hypothesize that SC directly interacts with human eosinophils and plays an important role in activation of this leukocyte. In this report, we demonstrate a unique function of SC as a costimulatory molecule for effector functions of human eosinophils. This interaction between SC and eosinophils may provide a novel mechanism to regulate mucosal tissue inflammation.

Youichi Motegi and Hirohito Kita

Department of Immunology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905

Received for publication April 6, 1998. Accepted for publication June 17, 1998. 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 Supported in part by Grants AI 34577 and AI 34486 from the National Institutes of Health and by the Mayo Foundation.

2 Address correspondence and reprint requests to Dr. Hirohito Kita, Department of Immunology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail address: kita.hirohito@mayo.edu

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0022-1767/98/$02.00

3 Abbreviations used in this paper: S-IgA, secretory IgA; FcγR, receptor for the Fc portion of IgA; DCs, defined calf serum; EDN, eosinophil-derived neurotoxin; GM, granulocyte-macrophage; HSA, human serum albumin; PE, phycoerythrin; SC, secretory component.
novel mechanism to regulate the magnitude of mucosal tissue inflammation.

Materials and Methods

Reagents
Human S-IgA was obtained from Organon Teknika-Cappel (Malvern, PA) or Accurate Chemical & Scientific (Westbury, NY). Purified human serum IgA and IgG were purchased from ICN Pharmaceuticals (Costa Mesa, CA). Purified human SC was kindly provided by Dr. Michael W. Russell (University of Alabama, Birmingham, AL). The IgG fraction of goat anti-human SC Ab and phycoerythrin (PE)-conjugated F(ab')2 fragments of donkey anti-goat IgG Ab were purchased from ICN (St. Louis, MO) and Jackson Immunoresearch Laboratories (West Grove, PA), respectively. mAb against human FceR (My43, mouse IgM) and control mAb (anti-ox erythrocyte, mouse IgG1) were generated by Dr. Li Shen (NJ Medical School, Hanover, NJ). Mouse anti-human CD18 mAb (mouse Ig1) and purified mouse IgG1, as a control, were purchased from Becton Dickinson (San Jose, CA) and ICN Pharmaceuticals, respectively. Recombinant human granulocyte-macrophage (GM)-CSF was purchased from Genzyme (Cambridge, MA). Recombinant human IL-5 was generously provided by Schering-Plough. Human serum albumin (HSA) and defatted calf serum (DCS) were from Sigma Chemical (St. Louis, MO) and HyClone Laboratories (Logan, UT), respectively. Human neutrophil elastase and elastase substrate (MeOSuc-Ala-Ala-Pro-Val-pNA) were purchased from Calbiochem-Novabiochem (La Jolla, CA).

Preparation of stimulii
Eosinophils were purified from peripheral blood obtained from normal volunteers as described previously (26). The percentage of eosinophils in peripheral blood of these donors was <5%. Briefly, heparinized venous blood was layered onto 1.085 g/ml Percoll (made in PIPES buffer from Inverted Medical Systems, Fullerton, CA) for 30 min. Plasma, mononuclear cells, and Percoll layers were removed, and erythrocytes were lysed by osmotic shock. The remaining eosinophil/neutrophil pellet was mixed with anti-CD16-bound immunomagnetic beads (Miltenyi Biotec, Sunnyvale, CA) and incubated for 1 h. The cells were then separated using a magnetic cell separation system (MACS; Miltenyi Biotec). The eluate was collected, and cell number and eosinophil purity were determined. Neutrophils were isolated using a gradient material, 1-Step Polymorphs (Accurate Chemical & Scientific), following the procedure recommended by the manufacturer. The purities of eosinophil and neutrophil preparations were >99%. All the isolation procedures were performed at 4°C or on ice.

Preparation of stimuli
Human S-IgA, serum IgA, and SC immobilized onto cytochrome c-activated Sepharose 4B beads (Sigma) or tissue culture plates were used as stimuli for eosinophils and neutrophils. Sepharose 4B beads were coupled to S-IgA or serum IgA, at a concentration of 5 mg protein/ml of packed beads, as previously described (24). To immobilize Ig or SC to tissue culture plates, 96-well flat-bottom tissue culture plates (Costar) were coated with 50 μl of indicated concentrations of S-IgA, serum IgA, or SC diluted in PBS (pH 7.4) overnight at 4°C. Plates were then blocked with 100 μl of DCS or 2.5% HSA diluted in PBS for 2 h at 37°C. After blocking, the wells were washed twice with 200 μl of PBS before use. In some experiments, the wells were coated with 50 μl of 0.5 μg/ml human recombinant IL-8 overnight at 4°C before being subsequently coated with 50 μl of SC or HSA (as a control) diluted at 10 μg/ml in PBS for 2 h at 37°C. These plates were blocked with 100 μl of 2.5% HSA and washed twice with 200 μl of PBS before use.

Degranulation assay
Degranulation of eosinophils and neutrophils was induced by Ig immobilized onto Sepharose 4B beads as described previously with minor modifications (24). Briefly, 96-well round-bottom tissue culture plates (Costar No. 3799) were blocked with 0.5% BSA, pH 7.4, and was expressed as nanomoles of cytochrome c reduction per 1 × 106 cells.

Flow cytometry analysis of SC binding
Binding of SC to eosinophils and neutrophils was examined by flow cytometry. Purified eosinophils or neutrophils (1 × 106 cells) were suspended in RPMI 1640 medium supplemented with 25 mM HEPES, 1% BSA, and 0.1% NaN3, and incubated with or without 30 μg/ml SC for 90 min on ice. Cells were washed twice with PAB buffer (PBS containing 0.1% NaN3, and 0.5% BSA, pH 7.4), and stained with 20 μg/ml goat IgG anti-human SC Ab for 30 min on ice, followed by 5 μg/ml PE-conjugated F(ab')2 fragment of donkey anti-goat IgG for 30 min on ice. The cells were then washed with PAB buffer and fixed with 1% paraformaldehyde in PBS (pH 7.4). The fluorescence intensity of individual cells was measured using a FACScan (Becton Dickinson, Mountain View, CA), and analyzed by Becton Dickinson lysis II software.

Binding of 125I-labeled SC
SC was radioiodinated by IODO-GEN Iodination Reagent (Pierce, Rockford, IL) according to the procedure recommended by the manufacturer. SC (63 μg) was labeled with 500 μCi of 125I, and the specific activity of labeled protein was 605 Ci/mmol. The binding of 125I-labeled SC to eosinophils was measured according to a method described previously for cytokines with minor modifications (33). Eosinophils (7 × 105 cells/sample) suspended in 50 μl of binding medium (RPMI 1640 medium supplemented with 25 mM HEPES, 1% BSA, and 0.1% NaN3, pH 7.4) were incubated with 50 μl of 12.5 nM 125I-labeled SC in the presence or absence of a serum dilution of unlabeled SC, S-IgA, or IgG for 2 h on a rotating table at 4°C. Cells were then overlayed onto 200 μl of DCS and centrifuged at 3000 rpm for 3 min. Pellets were frozen on dry ice and cut away from the supernatant. Radioactivity in the pellets was measured in a gamma counter (Packard, Downers Grove, IL).
IgA-beads released approximately twice the amount of EDN compared with serum IgA immobilized onto tissue culture wells. As shown in Figure 2, cells were stimulated with serial dilutions of S-IgA or serum IgA to assess direct comparison of eosinophils and neutrophils. Purified eosinophils and neutrophils from neutrophils stimulated with S-IgA-beads and serum IgA were coated with various concentrations of S-IgA or serum IgA and blocked with DCS. Isolated eosinophils or neutrophils were added to the wells, and superoxide production was measured by the reduction of cytochrome c as described in Materials and Methods. The results of superoxide production at 120 min of incubation are summarized. Data are presented as mean ± SEM from four independent experiments. *, significant differences (p < 0.05) compared with cells incubated with the same concentrations of serum IgA.

**Results**

**Effects of S-IgA and serum IgA on degranulation of eosinophils and neutrophils**

Previous studies suggested that both neutrophils (13–15) as well as eosinophils (16) possess FcεR. Therefore, we examined whether S-IgA and serum IgA induce effector functions of these two cell types. Purified eosinophils and neutrophils were stimulated with Sepharose 4B beads coated with S-IgA or serum IgA, and degranulation was assessed by measuring the amount of EDN (for eosinophils) and elastase (for neutrophils) in the supernatants. As shown in Figure 1, serum IgA-beads induced both EDN release from eosinophils and elastase release from neutrophils, consistent with the expression of FcεR on these two cell types (13–16). S-IgA-beads released approximately twice the amount of EDN compared with those stimulated with serum IgA-beads (p < 0.001). In contrast, there were no significant differences in elastase released from neutrophils stimulated with S-IgA-beads and serum IgA-beads. Thus, S-IgA is likely a more potent secretagogue than serum IgA for eosinophils but not for neutrophils.

Next, we examined whether another function of eosinophils, i.e., superoxide production, is stimulated with S-IgA. By using the same detection system, the superoxide production assay also allows direct comparison of eosinophils and neutrophils. Purified cells were stimulated with serial dilutions of S-IgA or serum IgA immobilized onto tissue culture wells. As shown in Figure 2, left, both S-IgA and serum IgA induced superoxide production from eosinophils in a concentration-dependent manner. The stimulatory effects of these Ig reached a plateau at 3 or 10 μg/ml. Striking differences were found in the amounts of superoxide released; S-IgA induced significantly larger amounts of superoxide production than serum IgA at the optimal concentrations (p < 0.05). At 10 μg/ml, eosinophils stimulated with S-IgA produced ~2.5-fold more superoxide compared with those stimulated with serum IgA. In neutrophils, both S-IgA and serum IgA induced superoxide production in a concentration-dependent manner; however, there was no difference between the magnitudes of neutrophil responses to S-IgA and to serum IgA at the optimal concentrations (Fig. 2, right). S-IgA induced less superoxide production than serum IgA at the suboptimal concentrations (p < 0.05 at 1 μg/ml). Altogether, these findings suggest that S-IgA stimulates eosinophil functions more potently than serum IgA. In contrast, S-IgA stimulates neutrophil functions similarly to or less potently than serum IgA.

**Binding of SC to eosinophils**

The presence of SC in S-IgA, but not in serum IgA, is notable (reviewed in Ref. 8). Therefore, we hypothesized that SC binds to eosinophils and activates their effector functions. To test this hypothesis, we first examined whether eosinophils are able to bind to SC by flow cytometry. Purified eosinophils were incubated with or without SC, and SC bound to the cells was detected by anti-SC Ab followed by fluorochrome-conjugated secondary Ab. As shown in Figure 3, in the absence of SC, minimal amounts of SC were detected on the surface of eosinophils. In the presence of SC, the binding was greatly increased, suggesting eosinophils do bind to SC. The geometric mean fluorescence intensity of samples stained with control Ab, anti-SC Ab (without SC), and anti-SC Ab (with

**Statistical analysis**

All results are shown as mean ± SEM from the numbers of experiments indicated. The statistical significance of the differences was assessed with Student’s paired t test.

![FIGURE 1](http://www.jimmunol.org/) Degranulation of eosinophils and neutrophils induced by S-IgA and serum IgA. Isolated eosinophils or neutrophils were incubated with medium alone ( ), Sepharose 4B beads coated with S-IgA ( ■) or serum IgA ( ) for 4 h. Eosinophil degranulation was quantified by measuring the concentration of EDN in the cell-free supernatant by RIA. Neutrophil degranulation was quantified by measuring the concentration of elastase in the cell-free supernatant by enzymatic assay. Data are expressed as mean ± SEM from six independent experiments. *, significant difference (p < 0.001) compared with eosinophils incubated with serum IgA.

![FIGURE 2](http://www.jimmunol.org/) Superoxide production by eosinophils and neutrophils stimulated with S-IgA or serum IgA. The wells of 96-well tissue culture plates were coated with various concentrations of S-IgA or serum IgA and blocked with DCS. Isolated eosinophils or neutrophils were added to the wells, and superoxide production was measured by the reduction of cytochrome c as described in Materials and Methods. The results of superoxide production at 120 min of incubation are summarized. Data are presented as mean ± SEM from four independent experiments. *, significant differences (p < 0.05) compared with cells incubated with the same concentrations of serum IgA.

![FIGURE 3](http://www.jimmunol.org/) Flow cytometric analyses of SC binding to eosinophils. Isolated eosinophils were incubated with or without SC (30 μg/ml) for 90 min on ice. After washing, the cells were stained with goat IgG anti-human SC (final concentration, 20 μg/ml), followed by PE-conjugated F(ab)\(_2\) fragments of donkey anti-goat IgG (final concentration, 5 μg/ml). The cells were then washed, fixed with 1% paraformaldehyde, and analyzed by flow cytometry. Controls indicated by shaded area are the cells incubated with goat IgG (isotype-matched control), followed by PE-conjugated F(ab)\(_2\) fragments of donkey anti-goat IgG. Histograms of one of three experiments showing similar results are presented.
SC) were 77.2 ± 9.2, 76.7 ± 9.3, and 116.2 ± 13.0, respectively (mean ± SEM, n = 3, p < 0.01 between “without SC” and “with SC”).

The specificity of SC binding to eosinophils was further examined by using 125I-labeled SC. Eosinophils were incubated with 125I-labeled SC in the presence or absence of serial dilutions of unlabeled SC, S-IgA, or IgA. As shown in Figure 4, when eosinophils were incubated with 12.5 nM 125I-labeled SC, substantial amounts of bound SC were detected. This binding of 125I-labeled SC was inhibited by unlabeled SC in a concentration-dependent manner, indicating specific binding of SC to eosinophils. Furthermore, the binding of 125I-labeled SC was also inhibited by unlabeled S-IgA in a concentration-dependent manner albeit not as potently as unlabeled SC. In contrast, binding of 125I-labeled SC was not inhibited by unlabeled serum IgA.

Effects of SC on eosinophil activation

GM-CSF activates effector functions of both eosinophils (34, 35) and neutrophils (36). Furthermore, IL-5 enhances various functions of eosinophils, such as degranulation, helminthotoxicity, and survival, and it is implicated in the pathophysiology of allergic diseases (reviewed in Ref. 37). GM-CSF and IL-5 can also induce superoxide production from eosinophils (38). Thus, we examined whether binding of SC to eosinophils leads to enhancement of their effector functions when stimulated with these cytokines. Eosinophils and neutrophils, as a control, were added to wells coated with SC in the presence or absence of cytokines; superoxide production was measured. As shown in Figure 5A, left, immobilized SC by itself did not induce eosinophil superoxide production up to 120 min; GM-CSF, 0.1 ng/ml, by itself induced moderate superoxide production; SC and GM-CSF worked synergistically and induced considerable superoxide production. In contrast, as shown in Figure 5A, right, GM-CSF induced minimal superoxide production from neutrophils, and immobilized SC did not enhance superoxide production. Figure 5B summarizes five experiments with a similar experimental design. Although immobilized SC by itself did not induce superoxide production from eosinophils, immobilized SC strikingly enhanced the eosinophil response to GM-CSF by 80% (mean of five experiments, p < 0.01). Likewise, eosinophil superoxide production stimulated with 1 ng/ml IL-5 was enhanced by immobilized SC by 92% (mean of five experiments, p < 0.01). In contrast, immobilized SC did not affect neutrophil superoxide production either in the presence or absence of GM-CSF.

The findings described above suggest that SC acts synergistically with other agonists (e.g., cytokines) to stimulate eosinophil function. As shown in Figure 6, this concept was further tested by coimmobilizing SC and IgG onto the wells of tissue culture plates. By itself, immobilized IgG induced superoxide production from both eosinophils and neutrophils. Eosinophil superoxide production stimulated with IgG was enhanced strikingly by SC coimmobilized to the wells (107 ± 18% of enhancement, mean ± SEM, 0.01 between "without SC" and "with SC").
In this study, we found that serum IgA stimulates degranulation and superoxide production by eosinophils and neutrophils (Figs. 1 and 2), and an anti-FcαR inhibits the eosinophil response (Fig. 7). These results are consistent with previous observations showing that both eosinophils and neutrophils express FcαR (13–16), bind IgA (14, 24, 40, 41), and can be stimulated through this receptor (14, 24, 42). However, eosinophil and neutrophil responses to S-IgA were strikingly different. In eosinophils, S-IgA induced more EDN release and superoxide production than serum IgA; but in neutrophils, S-IgA and serum IgA induced similar elastase release and S-IgA induced slightly less superoxide production than serum IgA. Compatible observations by others demonstrated that the eosinophil chemotactic response to IL-8 was enhanced by immobilized S-IgA but not by serum IgA (43). Furthermore, Staphylococcus aureus opsonized with serum IgA and S-IgA induced similar degrees of respiratory burst in neutrophils (42). Therefore, it is apparent that S-IgA stimulates functions of eosinophils more potently than serum IgA, and that S-IgA and serum IgA stimulate functions of neutrophils similarly.

This stronger stimulatory effect of S-IgA compared with serum IgA on eosinophils is unlikely due to the difference in binding efficiency of S-IgA and IgA to solid surfaces, such as Sepharose 4B beads or plastic plates, because the responses of neutrophils to immobilized S-IgA were similar to or slightly less than those to serum IgA (Figs. 1 and 2). The differences in the potencies of S-IgA and serum IgA cannot be explained by the differences in IgA isotypes, because eosinophils respond similarly to IgA1 and IgA2 (24). Thus, SC, which is bound to S-IgA but not to serum IgA, may activate eosinophil functions. In fact, we found that binding of purified SC to eosinophils was inhibited by S-IgA but not by serum IgA (Fig. 4). SC immobilized onto the tissue culture plates strikingly enhanced eosinophil superoxide production stimulated with cytokines, such as GM-CSF and IL-5 (Fig. 5), or IgG (Fig. 6); SC did not affect neutrophil superoxide production stimulated with GM-CSF or IgG. We also noted that SC by itself does not provoke eosinophil functions in the absence of other agonists. These findings suggest that, in eosinophils, SC acts synergistically with other agonists, such as cytokine and Ig, and stimulates their effector functions. In contrast, neutrophil function is not affected by SC even in the presence of other agonists. Thus, SC likely has a unique capacity to stimulate eosinophils specifically.

Then, how does SC activate eosinophil functions? Our previous studies suggest that adhesion molecules, especially β2 integrins, play crucial roles in eosinophil activation stimulated with cytokines or IgG (31, 32). Eosinophil superoxide production stimulated
with these agonists was strikingly enhanced when cells were able to adhere to substrates through the β2 integrins (31, 32). In this study, we found that β2 integrins were involved in eosinophil superoxide production after stimulation with S-IgA (Fig. 7B) but not with serum IgA (Fig. 7A). Furthermore, eosinophil superoxide production on SC-coated plates was also totally dependent on β2 integrins (Fig. 8). Therefore, β2 integrins play critical roles in up-regulation of eosinophil function by SC.

The remaining question is how SC stimulates eosinophil functions through β2 integrins. Although this issue is currently under study in our laboratory, we can discuss several possibilities. It is commonly accepted that integrins in a resting cell do not bind or bind weakly to their ligands and that cellular activation is required for firm interaction between integrins and their ligands (reviewed in Ref. 44). Furthermore, β2 integrins are often promiscuous, binding to various molecules (45). Therefore, the first possibility is that binding of SC may specifically stimulate the avidity of eosinophil β2 integrins. The second and more likely possibility is that SC may serve as a ligand for β2 integrins. In fact, SC stimulated eosinophil function only when eosinophils were stimulated with cytokines or Ig: this characteristic is similar to stimulus-dependent up-regulation of the ligand-binding capacity of integrins (44). Our Scatchard plot analysis also showed that the binding of 125I-labeled SC to resting eosinophils was largely of low affinity ($K_D > 100$ nM, data not shown). Furthermore, SC belongs to the Ig supergene family (23, 46), a structure shared by various ligands for integrins, such as ICAM-1 and VCAM-1. The results of our preliminary experiments to identify the receptor(s) for SC using Abs against known α-chains of β2 integrins, including CD11a, CD11b, and CD11c, have been inconclusive (data not shown). It is also possible that SC may bind to another newly discovered member of β2 integrins, αββ', or to an as yet unidentified member(s) of β2 integrins on eosinophils. Alternatively, SC may bind to different site(s) other than β2 integrins on eosinophils. In fact, Lamkhioued et al. (47) detected a 15-kDa SC-binding protein in eosinophils by immunoprecipitation and immunosorbent chromatography. While its identity is unknown as yet, this molecule is clearly another candidate.

Although the receptors for SC are not yet identified, our study clearly indicates that SC enhances the effector functions of eosinophils, but not those of neutrophils. Therefore, SC and S-IgA may play important roles in regulating eosinophil functions in vivo in diseases associated with mucosal eosinophilia and in various allergic diseases. Interestingly, allergen-specific S-IgA is increased in spuTa and nasal washing fluids from patients with asthma and ragweed hay fever, respectively (48, 49). Marked deposition of SC and S-IgA is found in skin tissues from patients with chronic eczema and atopic dermatitis (50). In addition, the presence of allergen-specific S-IgA in spuTa, but not of specific IgA in sera, was associated with asthma symptoms (48). The concentrations of released eosinophil granule protein in spuTa or bronchoalveolar lavage fluids correlated with the levels of S-IgA in patients with bronchial asthma (51) and chronic eosinophilic pneumonia (52), suggesting that S-IgA may in fact induce eosinophil degranulation in respiratory mucosa in vivo. Furthermore, S-IgA induces not only degranulation and superoxide, but also other effector functions of eosinophils, such as parasite killing (53), production of lipid mediators (e.g., platelet-activating factor) (54), and synthesis of cytokines (e.g., IL-4 and IL-10) (55). Thus, circumstantial evidence suggests an association between S-IgA and eosinophil activation in diseases. Therefore, further studies on the interaction among SC, S-IgA, and eosinophils may lead to a better understanding of the mechanisms of various mucosal and allergic diseases. Finally, IgA has recently been recognized as a unique Ig among the various isoatypes because of its restricted ability to use ancillary effector mechanisms, such as activation of complement, phagocytosis, and binding to effector cells (reviewed in Ref. 56). It would be interesting to know how eosinophils interacting strongly with S-IgA may fit into this global paradigm of IgA and mucosal immunology.

Acknowledgments

We thank Drs. M. W. Russell and L. Shen for providing us with purified human SC and anti-FcεRI mAb, respectively. We also thank Dr. G. J. Gleich for critical reading of the manuscript, Linda H. Arneson for secretarial assistance, and Cheryl Adolphson for editorial assistance.

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