

IgE Modulates Neutrophil Survival in Asthma: Role of Mitochondrial Pathway¹

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The high-affinity IgE receptor (FcεRI) has recently been reported to be expressed by neutrophils in atopic asthmatic individuals, leading to speculations that IgE could influence biological functions of these cells. In this study, we demonstrate that monomeric human IgE delayed spontaneous apoptosis of primary human neutrophils from atopic asthmatics in vitro. This effect was not dependent on FcεRI cross-linking or autocrine release of soluble mediators; however, it was associated with increased expression of the antiapoptotic myeloid cell leukemia-1 protein, retention of the proapoptotic molecule Bax in the cytoplasm, decreased release of Smac from mitochondria, and reduced caspase-3 activity. Taken together, our results indicate that in vitro IgE can delay programmed cell death of neutrophils from allergic asthmatics and this may possibly contribute to neutrophilic inflammation in atopic asthma. *The Journal of Immunology*, 2007, 178: 2535–2541.

Asthma is a chronic inflammatory disease that has increased in prevalence, morbidity, and mortality over the last four decades (1). Although there is growing evidence that neutrophils may play a role in pathogenesis of various forms of this disease (2–4), it is not clear what factors contribute to the activation and survival of neutrophils under these circumstances (3).

The high-affinity IgE receptor (FcεRI) has been shown to be present not only on the surface of mast cells and basophils, but also on monocytes, platelets, eosinophils, dendritic and Langerhans cells (5). Contrary to the widely accepted paradigm that binding of IgE to FcεRI is a passive presensitization step (6), recent reports have demonstrated that IgE alone can mediate a spectrum of effects including a significant survival effect on mast cells and monocytes through binding FcεRI (7–10).

We recently showed that a subpopulation of peripheral blood neutrophils from atopic asthmatic (AA)³ individuals express FcεRI that is functionally capable of binding to IgE (11). In this study, we demonstrate an antiapoptotic effect exerted by monomeric IgE on neutrophils in vitro, implying a potential mechanism contributing to accumulation and subsequent activation of neutrophils in allergic asthma.

Materials and Methods

Subjects

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Manitoba. Clinical diagnosis of allergy and mild asthma were determined by the following: 1) previous history of asthma with or without associated allergic rhinitis; 2) >15% improvement in forced expiratory volume in the first second after inhalation of salbutamol 200 μg from a metered-dose inhaler; and 3) wheal and flare (≥3 mm in diameter) to one or more common airborne allergens. Three days before blood sampling, the participants refrained from using all medications, including anti-inflammatory medications such as glucocorticoids, antihistamines, and antileukotrienes.

Isolation, purification, and culture of human peripheral blood neutrophils

Neutrophils were separated from heparinized peripheral blood as described previously (11) resulting in a purity >98% as determined by Wright-Giemsa staining. Isolated neutrophils at a density of 1 million/ml were treated with GM-CSF (10 ng/ml) (PeproTech) or monomeric IgE (100 ng/ml) (certified azide-free from Diatec) or left unstimulated for 18 h. All cultures were incubated at 37°C under 5% CO₂ in RPMI 1640 supplemented with 10% FBS and antibiotics (HyClone). FcεRI cross-linking and GM-CSFR neutralization were performed with 20 μg/ml murine anti-human IgE F(ab')₂ (BD Pharmingen) and 1 μg/ml anti-human GM-CSFR α-chain mAb (K12B7.17A; Chemicon), respectively. Fc portion of human IgE was a gift from Dr. H. J. Gould (King's College London, London, U.K.) and has been previously characterized (12). For signaling assays, cells were pretreated for 10 min with 10 μM SB203580 or 100 nM wortmannin (Calbiochem) before stimulation.

Assessment of apoptosis

Apoptosis was detected after 18 h of culture by annexin-V-FITC (BD Biosciences)/propidium iodide (PI) (Sigma-Aldrich) staining assay to detect early apoptotic cells (membrane intact cells with externalized phosphatidylserine residues; annexin-V positive), late apoptotic (apoptotic cells with compromised membrane integrity; PI positive) and nonapoptotic cells. Briefly, neutrophils were washed once in ice-cold PBS and resuspended in 100 μl of annexin-V binding buffer (140 mM NaCl, 2.5 mM CaCl₂, 1.5 mM MgCl₂, and 10 mM HEPES (pH 7.4)) containing annexin-V-FITC and PI (1 μg/ml) for 15 min. Analysis was performed by FACSscan (BD Biosciences) using CellQuest Pro software (BD Biosciences), and cells low in both annexin-V and PI were considered viable.

Cytospin preparations

A total of 1 × 10⁵ cells were deposited onto microscope slides by cytospin centrifugation (ThermoShandon) and fixed with 4% paraformaldehyde (Fisher Scientific) for 20 min at room temperature.

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³ Abbreviations used in this paper: AA, atopic asthmatic; PI, propidium iodide; Mcl-1, myeloid cell leukemia-1; Smac, second mitochondrial activator of caspases.

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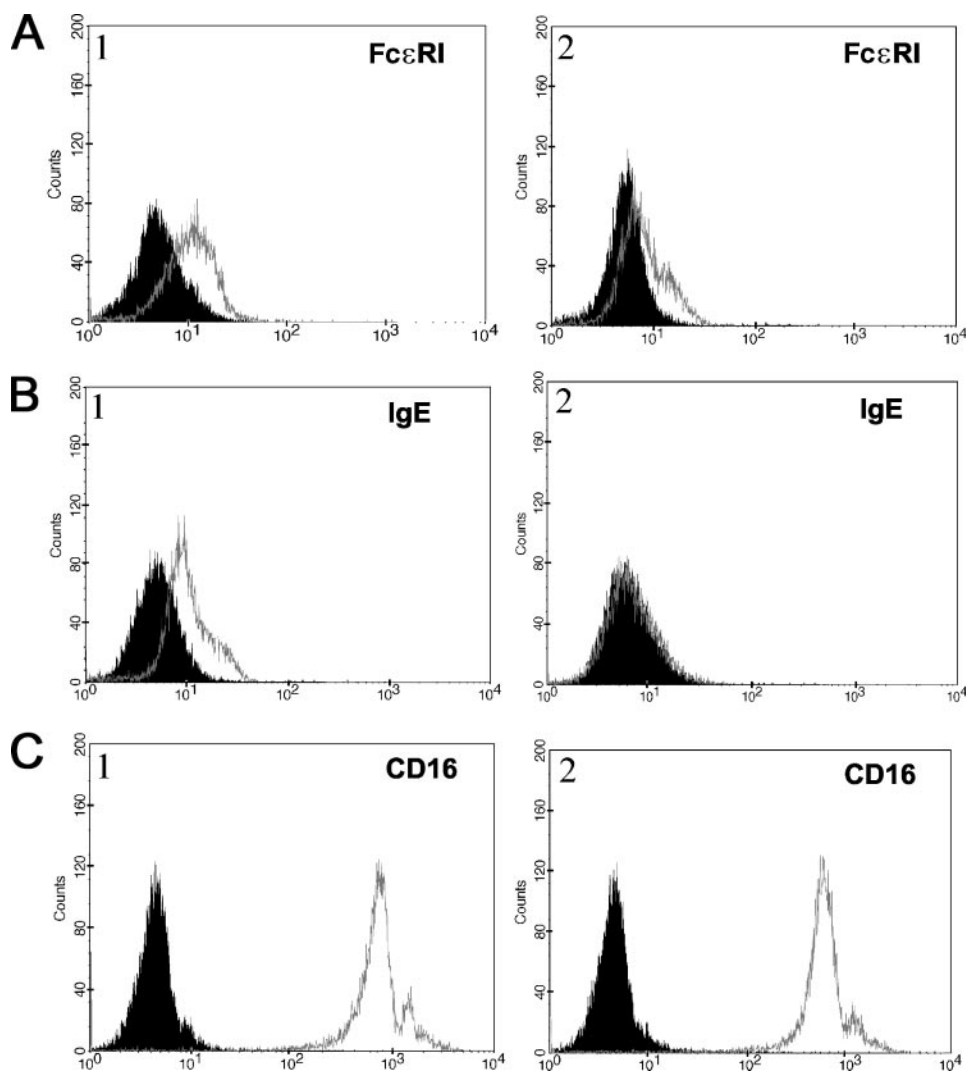


FIGURE 1. Neutrophils from AAs express FcεRI and carry surface-bound IgE. Freshly isolated neutrophils from two AAs (nos. 1 and 2) were analyzed for expression of FcεRI (A), surface-bound IgE (B), and CD16 (C) by FACS. Figure is representative of eight separate experiments.

Immunofluorescence and confocal laser scanning microscopy

Cytopreparations were washed in TBS and subsequently treated for 20 min with a universal blocking solution (DakoCytomation). Afterward, slides were briefly washed with TBS and incubated overnight at 4°C with polyclonal anti-human Bax Ab (10 µg/ml; DakoCytomation) or with the respective IgG control (Sigma-Aldrich) in Ab dilution buffer (DakoCytomation). After systematic washes, affinity-purified AlexaFluor 488 donkey anti-rabbit (10 µg/ml; Molecular Probes) was added for 1 h at room temperature. Slides were then extensively washed and counterstained for 5 min with PI (10 µg/ml). Following lengthy washes, slides were mounted with ProLong antifade agent (Molecular Probes) and covered with a coverslip before being acquired by an Olympus FluoView confocal laser scanning microscope and analyzed with the FluoView software.

Bax aggregation

At least 300 cells were counted per slide, and percentages of cells with aggregated Bax (as shown in Fig. 4C) was determined by two independent observers.

Western blots and subcellular fractionation

Immunoblotting (11) and subcellular fractionation (13) were performed as previously described. Abs used were as follows: rabbit polyclonal anti-actin (Sigma-Aldrich), anti-myeloid cell leukemia-1 (Mcl-1), anti-Bax (DakoCytomation), anti-Smac (BD Biosciences), anti-XIAP (Cell Signaling Technology), and mAb anti-manganese superoxide dismutase (BD Biosciences).

Densitometry analysis

The intensity of bands was determined using AlphaEase FC software version 3.1.2 relative to control loading levels.

Caspase-3 activity assay

Caspase-3 enzymatic activity was acquired by an EG&G Berthold microplate luminometer using the Caspase-Glo-3 (Promega) assay according to the manufacturer's instructions.

ELISA

Cytokine concentrations in the culture supernatant were determined according to basic laboratory protocols. Purified anti-human capture and biotinylated detection Abs were as follows: IL-6 (5&7IL6), IL-8 (3IL8-H10, I8-S2) (Endogen), and Fas ligand (100419 and BAF126; R&D Systems).

FACS analysis

Abs used for flow cytometry were as follows: mAb anti-human FcεRIα-chain (CRA-I; provided by Dr. C. Ra, Juntendo University, Tokyo, Japan), mAb anti-human IgE (BD Biosciences), AlexaFluor 488 rabbit-mouse F(ab')₂ (Molecular Probes), FITC-mAb anti-human CD16, mAb and FITC-mAb IgG1 (Sigma-Aldrich), and FITC-mAb anti-Fas (DakoCytomation). Flow cytometric analysis was performed using FACSCalibur and CellQuest software (BD Biosciences).

Statistics

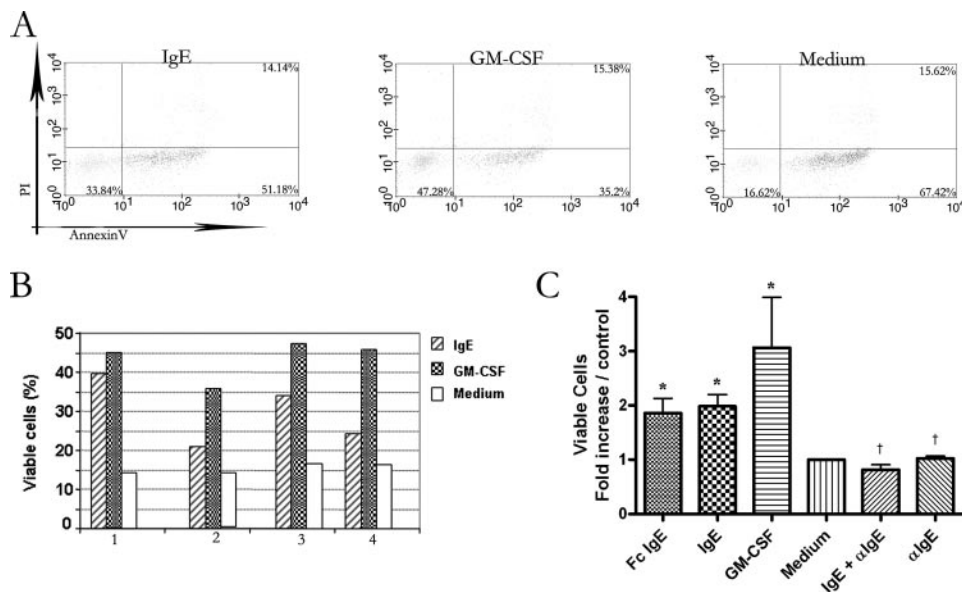
Statistical analysis was performed using one-way ANOVA and Mann-Whitney *U* tests. A *p* value <0.05 was considered statistically significant.

Results

Neutrophils from AAs express the FcεRI and bind IgE

In this study, we first confirmed that neutrophils isolated from the peripheral blood of volunteer AAs expressed the FcεRI (Fig. 1A). These cells were also monitored for the amount of cell-bound IgE

FIGURE 2. IgE inhibited apoptosis of neutrophils of AA individuals. *A*, AA neutrophils were incubated with medium alone, IgE, or GM-CSF for 18 h and analyzed by FACS in the three groups. Nonapoptotic cells appear as annexin-V PI low ($n = 8$). *B*, Viability of neutrophils from four AA subjects after 18 h of culture with medium alone, IgE, or GM-CSF. *C*, Fc ϵ RI cross-linking by adding anti-IgE to IgE did not mediate neutrophil survival after 18 h of culture. Mean value for the medium group served as a reference ($n = 3-8$; *, $p < 0.01$; †, $p > 0.05$).



on their surface at the time of purification (Fig. 1*B*). The portion of cells in the neutrophil pool that expressed Fc ϵ RI varied among AA patients to some extent (mean surface expression $47.67 \pm 5.46\%$; $n = 8$); whereas a ubiquitous surface marker such as CD16 was abundantly present on the cell surface (Fig. 1*C*). Moreover, the amount of IgE bound on the surface of these cells also differed from one asthmatic to another (Fig. 1*B*). In accord with previous publications (11), no surface expression of Fc ϵ RI was detected in neutrophils from healthy individuals (data not shown).

IgE delayed programmed cell death of neutrophils from AA subjects

In this step, AA neutrophils were exposed to monomeric IgE (100 ng/ml) or left untreated for 18 h, and then assessed for apoptosis. GM-CSF (10 ng/ml) was used as a positive control for inhibition of neutrophil apoptosis. Interestingly, IgE and GM-CSF significantly enhanced neutrophil survival as compared with medium alone (1.9 ± 0.3 and 3 ± 0.8 -fold increase, respectively; $p < 0.05$) (Fig. 2). This suppression of apoptosis was apparent in the

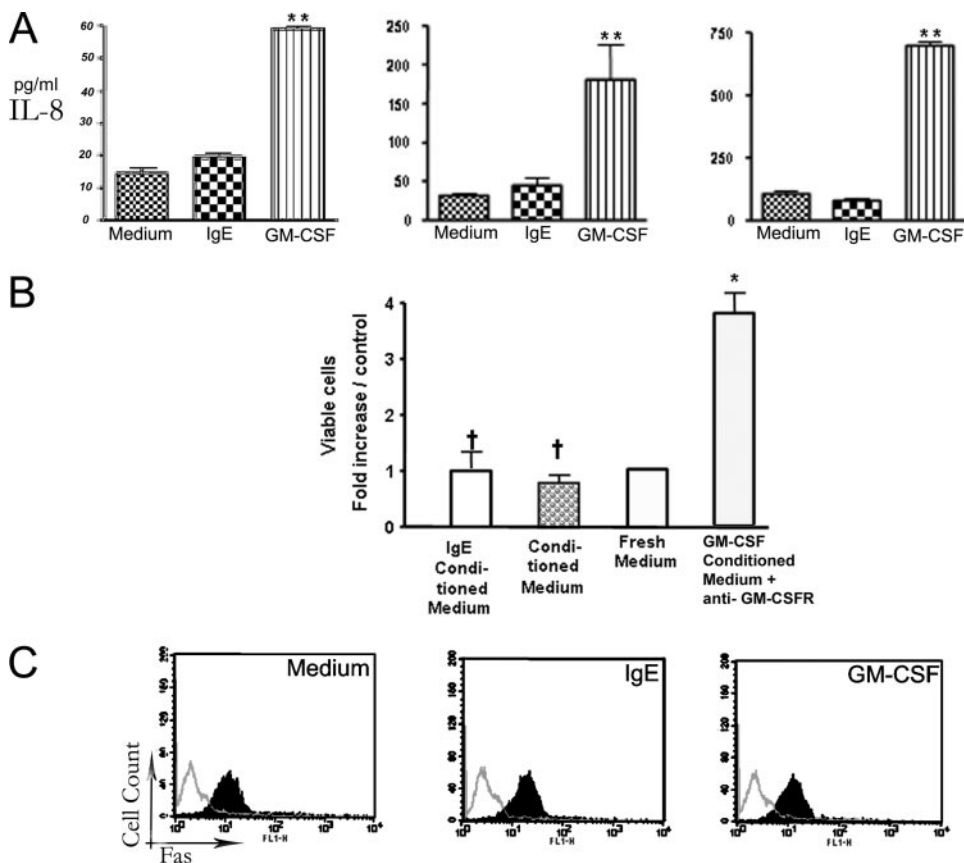


FIGURE 3. IgE inhibited neutrophil apoptosis independently of soluble factors or levels of Fas. *A*, The level of IL-8 (mean $\pm$ SEM) was measured by ELISA in triplicates of four dilutions in cell-free supernatants from 18-h neutrophil cultures of three AA individuals. Each graph represents a separate experiment (**, $p < 0.01$ compared with medium). *B*, Survival of neutrophils from three healthy individuals after an 18-h culture with fresh medium or conditioned medium from neutrophils of three allergic asthmatics. Neutralizing Ab to GM-CSFR α -chain was added before resuspending cells in GM-CSF-conditioned medium (*, $p < 0.01$; †, $p > 0.05$). Mean value for the fresh medium group served as a reference. *C*, Expression of Fas (CD95) (closed histogram) against isotype control (open histogram) in neutrophils after 18 h of culture. Panel represents one of three independent experiments.

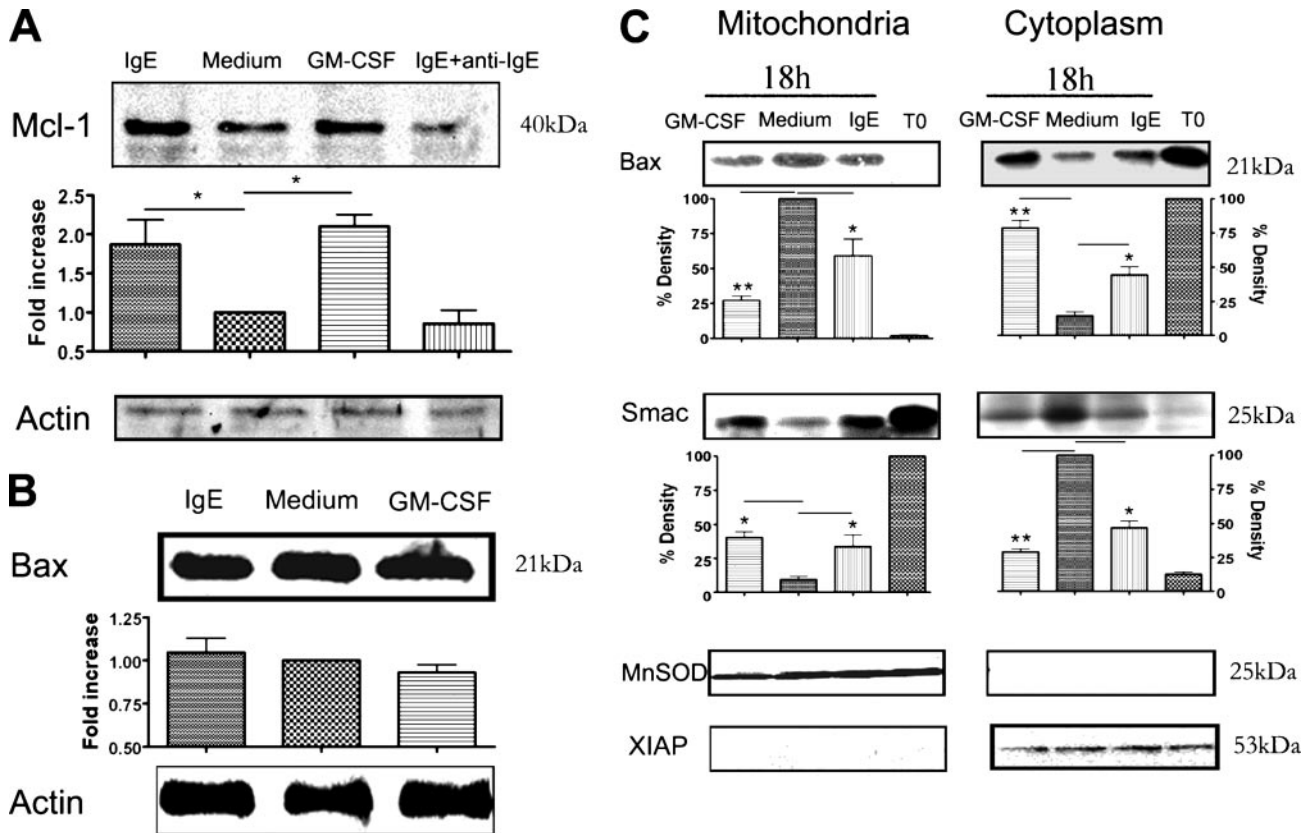


FIGURE 4. IgE prevented neutrophil apoptosis: the mitochondrial pathway. Figure represents three separate experiments in which IgE and GM-CSF up-regulated Mcl-1 protein (A; $p < 0.05$), but Bax protein levels were not substantially altered (B). Immunoblotting was performed on total cell lysates after 18 h of culture. Membranes were reprobed with anti-actin Ab to ensure equal loading. Densitometry values for medium served as a control. C, Cytosolic and mitochondrial lysates of fresh neutrophils (T0) or cells cultured for 18 h were immunoblotted for Bax and Smac. Manganese superoxide dismutase (MnSOD) and XIAP served as mitochondrial and cytosolic content reference, respectively. Densitometry values for medium or T0 served as 100% reference (*, $p < 0.05$; **, $p < 0.01$).

redistribution of cell-bound annexin-V and the percentage of cells that were PI positive (compromised membrane integrity) (Fig. 2A).

Higher concentrations of IgE (1 and 10 $\mu\text{g/ml}$) did not significantly enhance or compromise this antiapoptotic effect; however, in contrast to IgE, human IgG (100 ng/ml) had no influence on neutrophil survival, confirming the specificity of IgE's effect. Furthermore, monomeric IgE by itself had no effect on apoptosis of neutrophils from healthy donors (data not shown).

To verify that the inhibition of apoptosis was not due to the particular IgE batch used or the Fab portion of the IgE molecule, neutrophils from AAs were incubated with the Fc fragment of human IgE (100 ng/ml) for 18 h and assessed for apoptosis. As demonstrated in Fig. 2C, the Fc fragment of IgE resulted in a similarly delayed apoptosis of neutrophils from these patients, but not from healthy controls (data not shown).

IgE-induced survival of neutrophils was not dependent on Fc ϵ RI cross-linking

Next, we examined whether Fc ϵ RI aggregation would also increase the life span of these cells. Whereas IgE or GM-CSF-stimulated neutrophils exhibited a significantly higher survival over the control ($p < 0.01$), cross-linking of Fc ϵ RI by anti-human IgE following IgE stimulation (>40% of cells were Fc ϵ RI positive; data not shown) abrogated IgE-induced survival of neutrophils ($n = 3$; Fig. 2C). Taken together with the above data, simple receptor occupancy by monomeric IgE but not receptor cross-linking was able to suppress apoptosis of AA neutrophils.

IgE enhanced neutrophil survival independently of soluble factor release or Fas/Fas ligand expression levels

To determine whether IgE enhanced neutrophil survival by auto-crine secretion of mediators, we first analyzed cell-free supernatants from the culture of IgE-stimulated cells for release of IL-6 and IL-8 that have been shown to extend neutrophil survival (14). The levels of IL-8 (Fig. 3A) as well as IL-6 (data not shown) in IgE-stimulated cultures were similar to control unstimulated cultures.

Although these results demonstrated that IL-8 and IL-6 were not involved in IgE-mediated neutrophil survival in allergic asthmatics, they did not exclude the role of numerous other soluble factors in this phenomenon. Therefore, we performed an experiment using conditioned medium from AA neutrophil cultures (>40% Fc ϵ RI expression; data not shown) stimulated for 18 h with GM-CSF, and medium with or without IgE. An 18-h incubation of freshly isolated populations of neutrophils from three normal individuals (no Fc ϵ RI expression; data not shown) with conditioned medium from IgE-stimulated and nontreated cell cultures did not influence survival any differently than new medium. However, GM-CSF-conditioned medium significantly increased neutrophil life span even in the presence of neutralizing Ab to GM-CSF α receptor ($p < 0.01$; Fig. 3B).

We also measured the expression levels of cell surface Fas (CD95) in neutrophils of AA subjects stimulated with IgE, GM-CSF, or medium alone by flow cytometry after 18 h of incubation. No significant differences in Fas expression were observed among

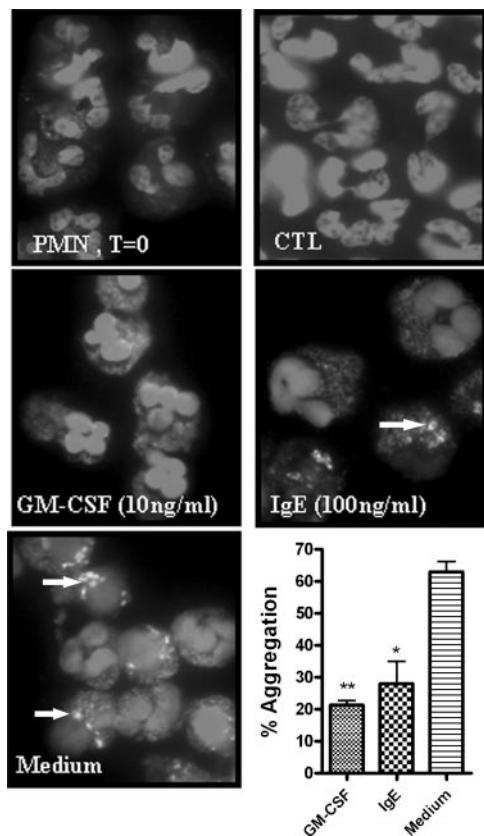


FIGURE 5. IgE prevented Bax aggregation. After 18 h, the punctate cytosolic distribution of Bax observed in fresh neutrophils (T0) was maintained by GM-CSF, and by IgE to some degree, whereas in the medium group the majority of cells exhibit Bax aggregation (arrows), indicating its activation and oligomerization. Nuclei were counterstained with PI. Original magnification, $\times 600$. The mean percentage of cells showing aggregation of Bax was determined according to *Materials and Methods* ($n = 3$; *, $p < 0.05$ and **, $p < 0.01$ compared with medium).

the three groups (Fig. 3C) (mean fluorescence intensity: 8.8 ± 1.5 vs 8.5 ± 1.6 and 8.7 ± 1.4 , respectively; $n = 3$). Moreover, the amount of soluble Fas ligand released in conditioned medium from all three groups was insignificant (lower than detection limit of 31.8 pg/ml, ELISA; data not shown).

IgE up-regulated Mcl-1 and inhibited Bax translocation to the mitochondria

The Bcl-2 family of proteins comprises important regulators of the mitochondrial pathway of apoptosis that include both pro- and antiapoptotic molecules (14). We examined the possible involvement of this family of molecules in the inhibition of neutrophil apoptosis by IgE.

Cell lysates from AA neutrophils stimulated with IgE and GM-CSF contained increased amounts (2-fold; $p < 0.05$) of the antiapoptotic Mcl-1 protein as determined by immunoblotting (Fig. 4A). Interestingly, although the total cellular Bax content did not change significantly after IgE or GM-CSF stimulation in our immunoblots (Fig. 4B), there was a clear reduction in mitochondrial Bax content and retention of cytosolic Bax that suggested prevention of Bax translocation (Fig. 4C). This finding was further supported by lower frequency of cells that demonstrated aggregation of Bax after 18 h of culture with GM-CSF (3-fold reduction; $p < 0.01$) or IgE (2-fold decrease; $p < 0.05$) compared with medium alone (Fig. 5).

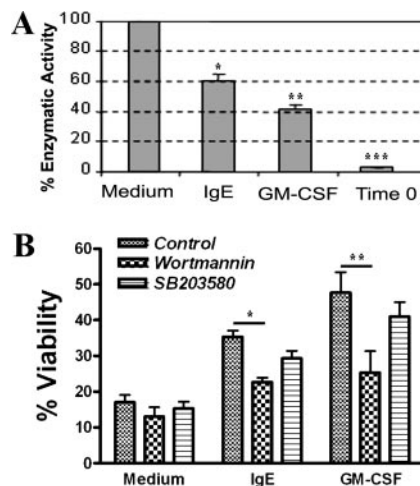


FIGURE 6. A, IgE down-regulated caspase-3 activity. Fresh neutrophils (time 0) or cells cultured for 18 h in the three groups were analyzed for executioner caspase-3 enzymatic activity. The mean value for the medium group served as 100% reference (mean $\pm$ SEM of three separate experiments) (*, $p < 0.05$, **, $p < 0.01$, and ***, $p < 0.001$ compared with medium). B, IgE prevented apoptosis through PI3K and p38 MAPK pathways. Neutrophils were preincubated with wortmannin and SB203580, cultured for 18 h, and then analyzed for apoptosis ($n = 5$; *, $p < 0.05$ and **, $p < 0.01$).

IgE decreased release of second mitochondrial activator of caspases (Smac) and suppressed caspase-3 activity

Smac is an inner-membrane mitochondrial protein that is released into the cytosol after loss of mitochondrial membrane integrity (15). As shown in Fig. 4C, treatment of neutrophils with GM-CSF and IgE significantly reduced release of Smac into the cytosol ($p < 0.05$). In accord with sequestration of mitochondrial Smac, significant decreases of ~ 40 ($p < 0.05$) and 60% ($p < 0.01$) were observed in caspase-3 enzymatic activity after an 18-h stimulation of AA neutrophils with IgE and GM-CSF, respectively, compared with medium alone (Fig. 6A).

The antiapoptotic effect of IgE was mediated via PI3K and p38 MAPK pathways

Caspase-3 activity in neutrophils correlates with the phosphorylation status of p38 MAPK (16). Preliminary study of signaling events in our system indicated involvement of p38, and PI3K. Although pretreatment of AA neutrophils with p38 MAPK inhibitor SB203580 partially suppressed IgE-induced survival, PI3K inhibitor wortmannin nearly abrogated ($p < 0.05$) this survival effect (Fig. 6B).

Discussion

To date, three types of IgE receptor have been identified in neutrophils: galactin 3 (Mac-2/εBP) (17), the low-affinity receptor (FcεRII/CD23) (18), and the high-affinity FcεRI (11). FcεRI binds IgE with a much higher affinity (> 1000 -fold) than FcεRII (19) and in AA neutrophils IgE primarily binds FcεRI (11).

Association of atopic disease with IgE/FcεRI has been described in many studies, and elevated serum IgE levels correlate with the severity or occurrence of asthma (20, 21); It is also worth noting that not only do IgE/FcεRI contribute to atopic disorders, but allergic conditions per se can also lead to an enhanced but heterogeneous expression of FcεRI in Langerhans cells (22) and monocytes (23) in atopic dermatitis lesions. In a similar manner,

AA individuals have circulating neutrophils that nonuniformly exhibit Fc ϵ RI on their surface (11). Unpublished data from our laboratory suggest that expression of Fc ϵ RI in neutrophils is under the regulation of Th2 cytokines. Fc ϵ RI is absent from neutrophils of healthy individuals, is frequently expressed in neutrophils of AAs, and less frequently observed in atopic nonasthmatics. Additionally, neutrophils isolated during the allergic season express higher levels of Fc ϵ RI, and carry more surface-bound IgE (M. P. Alphonse and A. S. Gounni, unpublished data).

Traditionally, Fc ϵ RI has been implicated in the release of mediators from mast cells after receptor cross-linking (5). Recent evidence from the literature has introduced a novel function for Fc ϵ RI, namely suppression of apoptosis, which occurs with simple receptor occupancy and does not necessarily require receptor aggregation (7–10). Data from the present study indicate a prosurvival effect of monomeric IgE that does not require receptor cross-linking. This effect is especially interesting because an IgE concentration as low as 100 ng/ml, the lower limit of concentrations found in atopic individuals (19), was capable of significantly inhibiting neutrophil apoptosis. It is worth mentioning that the impact of IgE on neutrophil survival varied among AA individuals to some extent. This may be explained by the variability of Fc ϵ RI expression in neutrophils as depicted previously (11). Another factor is prior *in vivo* binding of IgE to the receptor that might prevent exogenous IgE from binding after purification, although samples for this study were selected to carry minimal levels of prebound surface IgE. Interestingly, in 18-h cultures with medium, asthmatic neutrophils replete with prebound surface IgE did not always survive longer than asthmatic neutrophils without prebound IgE (data not shown). This may reflect the complex nature of asthma and regulation of neutrophil survival by a multitude of pro- and anti-inflammatory agents present in the asthmatic milieu.

Neutrophilic inflammation is often reported in asthma (2, 4) and even individuals with mild atopic asthma show increased lung biopsy neutrophil counts during seasonal allergen exposure (24) and after segmental challenge (25). Taken together with up-regulated Fc ϵ RI expression in neutrophils of AA individuals during the allergic season (M. P. Alphonse and A. S. Gounni, unpublished data), it is tempting to speculate that enhanced expression of Fc ϵ RI in AA neutrophils combined with high levels of IgE may prolong neutrophil survival, consequently accentuating neutrophilic inflammatory responses in allergic asthma.

Whether or not receptor cross-linking is required for IgE to exert an antiapoptotic effect has been a matter of controversy. Although the two initial studies on this issue have reported no survival effect after Fc ϵ RI cross-linking (7, 8), another study claimed that Fc ϵ RI-mediated degranulation led to mast cell survival (26). Kitaoura and colleagues (9) reported mast cell survival after Fc ϵ RI cross-linking with some forms of IgE but not with others. In the latter study, IgE molecules could be either “poorly” or “highly” cytokinergic and induced either minor or major receptor aggregation, with consequent differences in cytokine production and degree of mast cell survival; however, even when using the so-called poorly cytokinergic IgE molecules, Kitaoura et al. (9) detected a prosurvival effect that was independent of receptor aggregation or cytokine secretion. In monocytes, binding of IgE to Fc ϵ RI leads to survival, with or without receptor aggregation (10). Findings of the present study indicate that receptor occupancy, rather than cross-linking, is associated with higher levels of survival in neutrophils.

Transcriptional activity in neutrophils is generally deemed to be minimal (27). Nevertheless, these cells have the capacity to produce a number of soluble mediators (28), and conditioned medium from neutrophils treated with potent proinflammatory agents such as GM-CSF and LPS can inhibit neutrophil apoptosis (29). In this

study, conditioned medium from IgE-treated neutrophils did not inhibit apoptosis of freshly isolated cells. Moreover, levels of IL-8 and IL-6 were similar in supernatants from IgE-stimulated and unstimulated cells. Compared with data from GM-CSF conditioned medium, these findings argue against autocrine secretion of mediators as the major mechanism through which IgE mediated survival of AA neutrophil; however, based on our experiments, we cannot rule out the possibility that IgE might cause release of small amounts of other mediators (30) during early time points of culture with IgE.

Current evidence does not support a role for the extrinsic pathway of apoptosis (31) in programmed death of neutrophils because neutrophils from CD95 (Fas)-deficient mice have previously been shown to constitutively undergo apoptosis at the same rate as wild-type mice (32). In agreement with previous reports in mast cells and monocytes (7, 10), our results also imply that IgE-mediated inhibition of apoptosis is independent of Fas/Fas ligand expression levels.

Alteration of neutrophil apoptosis by the majority of factors studied so far seems to happen at the mitochondrial level (31). The Bcl-2 family of proteins comprises important regulators of this pathway and includes both pro- and antiapoptotic molecules. The proapoptotic members such as Bax and Bak function by translocating from the cytosol into the outer mitochondrial membrane where they oligomerize, penetrate and trigger cytochrome *c* release and subsequent caspase activation. In contrast, Mcl-1, one of few antiapoptotic proteins identified in neutrophils so far, has a role in maintaining mitochondrial membrane integrity (14). Study of various factors that delay neutrophil apoptosis has demonstrated a correlation between Mcl-1 levels and viability (33). In this study also, higher levels of AA neutrophil survival following incubation with IgE correlated with increased Mcl-1 content of these cells. Furthermore, enhanced expression of Mcl-1 was in agreement with the impaired translocation and aggregation of Bax into mitochondria and decreased release of Smac into the cytoplasm. These findings suggest that following stimulation with IgE, increased Mcl-1 levels may bind Bax and prevent its activation, resulting in maintained mitochondrial membrane integrity. In the virtual absence of cytochrome *c* from neutrophils (34), mitochondrial sequestration of Smac is then particularly important in keeping caspases at bay (35), suppressing apoptosis.

In conclusion, our data shed light on new aspects of neutrophil apoptosis in allergic asthma, and provide a potential mechanism by which IgE may accentuate neutrophilic inflammation in allergic asthma.

Disclosures

The authors have no financial conflict of interest.

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