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Potential Contribution of IL-7 to Allergen-Induced Eosinophilic Airway Inflammation in Asthma

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The primary function of IL-7 is to promote maturation and survival of T cells. Through microarray expression analysis, we previously observed that human blood eosinophils express mRNA for IL-7Ra (CD127) and its common γ chain (CD132). The purpose of this study was to determine whether eosinophils have functional IL-7 receptors and to assess the potential contribution of IL-7 to eosinophilic airway inflammation by evaluating its presence in bronchoalveolar lavage (BAL) fluid of subjects with atopic asthma before and after segmental bronchoprovocation with allergen. Immunoblot analysis revealed that CD127 is present in highly purified human blood eosinophils. Furthermore, eosinophils responded to IL-7 with phosphorylation of STAT5, up-regulation of the activation marker CD69, and prolonged survival. Neutralization of GM-CSF but not IL-5 significantly blunted these functional responses, suggesting that IL-7 mediates its effects by promoting eosinophil release of autologous GM-CSF. Notably, the suppressive effect of anti-GM-CSF on STAT5 phosphorylation occurred within 10 min of eosinophil exposure to IL-7. Thus, IL-7 likely activates eosinophil release of preformed rather than newly synthesized GM-CSF. The biological relevance of IL-7 to eosinophilia in vivo was implicated in a study of airway allergen challenge in patients with allergic asthma. IL-7 concentrations in BAL fluid increased significantly 48 h after segmental allergen challenge and were highly correlated with BAL eosinophils (r = 0.7, p < 0.001). In conclusion, the airway response to allergen is associated with the generation of IL-7, which may contribute to airway inflammation by promoting enhanced eosinophil activation and survival. Activation of eosinophils is a novel function for IL-7. The Journal of Immunology, 2009, 182: 1404–1410.

Interleukin-7 is required for T cell development in the thymus. In fact, a human mutation in the α-chain of the IL-7Ra (CD127) results in a SCID phenotype characterized by a lack of T cells, with no discernible effect on NK cells or B cells (1, 2). After thymic development, IL-7 is important for the homeostasis of naive T cell populations and for the generation and survival of memory CD4+ T cells (3). Because of its potent effect on survival and expansion of T cell populations, IL-7 is being developed as a therapeutic agent for T cell reconstitution (4–6) and neutralization of IL-7 has been suggested as a potential therapeutic for diseases such as rheumatoid arthritis, inflammatory bowel disease, atherosclerosis, multiple sclerosis, and solid epithelial tumors (7–11). IL-7 is produced primarily by epithelial cells and is found predominantly in the thymus, bone marrow, and intestine (12).

The receptor for IL-7 is composed of a 60–90 kDa cytokine-specific α-chain (IL-7Ra/CD127) and a 72-kDa common γ chain (γc)3 (CD132) that is the primary signaling component for the IL-7Rα as well as IL-2, IL-4, IL-9, IL-15, and IL-21 receptors in several cell systems (12). Dimerization of IL-7Ra/γc activates their associated kinases Jak1 and Jak3, respectively, with activation of STAT5 being a primary downstream signaling event (12).

In addition to T cells, there are scattered reports of CD127 expression or cellular responsiveness to IL-7 by other cell types including human peripheral monocytes (13), endothelial cells (14), fibroblasts (15), and eosinophil progenitors in the bone marrow (16). Through a microarray analysis of eosinophil gene expression, we previously observed that human blood eosinophils express mRNA for CD127 and CD132 (17). However, the expression of functional IL-7Ra on mature circulating eosinophils has not been reported.

Eosinophils are associated with allergic diseases including asthma and are elevated in the lung after allergen exposure. Eosinophils are thought to contribute to airway obstruction, hyperresponsiveness, and tissue remodeling that are characteristic of asthma (18). Furthermore, there is growing evidence that human (19–21) as well as murine (22) eosinophils are important regulators of T cell recruitment and function.

The purpose of the current study was 2-fold. First, using in vitro studies, we aimed to determine whether highly purified human blood eosinophils express functional IL-7Ra receptors and to characterize the response of eosinophils to IL-7. Second, we sought to determine whether IL-7 is present in the airway of atopic subjects with asthma, whether it is enhanced by airway allergen challenge, and whether levels of IL-7 are associated with airway eosinophilia. Our overarching hypothesis was that IL-7 contributes to allergic inflammation.
airway inflammation associated with asthma through activation of eosinophils.

Materials and Methods

Human subjects

For the ex vivo analysis of IL-7R function on human eosinophils, peripheral blood was obtained from normal or allergic donors. Subjects for the bronchoscopy study were allergic (skin prick test positive), with mild bronchial asthma (obstructive spirometry demonstrated a prebronchodilator FEV1 <80% of predicted). Allergens used in SBP were cat allergen (Fel d1; Bayer Allergy Products), ragweed (GR Ragweed mix; Greer Labs), and house dust mite (Der matophagoides farinae; Miles Allergy Products) based on each subject’s skin test reactivity and history. The bronchoalveolar lavage (BAL) was obtained from the subjects included monoclonal anti-human IL-7 (clone BVD10-40F6; BD Pharmingen) or anti-IL-5 Ab (clone 14611.3; R&D Systems) were used at a concentration of 20 ng/ml. Each experimental condition was tested in duplicate or triplicate.

Eosinophil viability was determined at 0, 48, and 72 h by trypan blue exclusion. At 0 h, the contents of three individual wells were counted. To obtain an accurate determination of cell survival, a consistent method for collecting and counting cells was established. Cell suspensions were pipette-mixed 25 times with a 100-μl pipetman. A 1/11 dilution of cells and trypan blue (0.4%) was prepared, pipette-mixed 12 times, and 10 μl was added to a hemacytometer. The number of viable and dead cells was determined in 8 x 1-mm2 areas of the counting chamber. Survival was determined by dividing the number of live cells at each time point by the number of live cells at 0 h and multiplying by 100. In PBMC “add back” experiments, eosinophil viability was determined by exclusion of propidium iodide (3 μg/ml) using flow cytometric analysis.

Flow cytometric analysis

For cell surface analysis of CD69, 1 x 106 eosinophils were stained using PE-conjugated anti-CD69 (clone TP1.55.3; Immunotech-Beckman Coulter) as previously described (23). Propidium iodide (3 μg/ml) was added to the stained cellular suspensions before analysis to allow electronic omission of any dead cells.

Detection of intracellular phospho-STAT5 by flow cytometric analysis was performed as previously described (19). In brief, purified blood eosinophils were incubated with 50 nM IL-7 for 15 min, fixed with 2% paraformaldehyde, permeabilized, and stained with PE-conjugated anti-phospho-STAT5 (Tyr 694; clone 47; BD Biosciences) or mouse IgG isotype control (BD Biosciences). Cells were analyzed by a BD FACSCaliber or FACScan II using 488 nm wavelength laser excitation. Eosinophil populations were gated as previously described (23), and 5000–10,000 photo-electric events were recorded. Data analyses were performed with CellQuest version 3.3 software (BD Biosciences).

Immunoblotting

For analysis of STAT5 phosphorylation, purified eosinophils were stimulated for 10 and 20 min in the presence or absence IL-7 (50 nM), and cell lysates were prepared as previously described (24). In some experiments, eosinophils were pretreated with neutralizing Ab to GM-CSF (Biosource International) or anti-IL-7 Ab (clone BVD10-40F6; BD Pharmingen). Purified blood eosinophils from seven blood donors or T cells from a single donor were prepared in lysis buffer (20 mM Tris (pH 7.4), 137 mM NaCl, 1 mM EDTA, 1 mM sodium ortho-vanadate, 20 mM β-glycerophosphate, 10 mM sodium fluoride, 1% Nonidet P-40, 0.25% deoxycholate, and 0.1% SDS) and insoluble material was removed by centrifugation at 15,800 x g for 10 min at 4°C. The soluble fraction was assayed for total protein and immunoblotted as previously described (24). Briefly, samples were resolved by SDS-PAGE, and proteins were transferred to a polyvinylidene difluoride membrane and probed with Ab specific for tyrosine-phosphorylated STAT5 (anti-pSTAT5A/B (Y694/Y699) Ab, catalog no. 9351; Cell Signaling Technology). Detection of immunoblotting was performed using Super Signal West Dura or Femto Chemiluminescent Substrate (Pierce). Equal protein loading was assured by densitometry analysis using NIH Image software.

Segmental bronchoprovocation (SBP) with allergen and bronchoalveolar lavage (BAL)

SBP with allergen and BAL were performed as previously described (25, 26). Allergens used in SBP were cat allergen (Fel d1; Bayer Allergy Products), ragweed (GR Ragweed mix; Greer Labs), and house dust mite (Der matophagoides farinae; Miles Allergy Products) based on each subject’s skin test reactivity and history. The IL-7R was shown to be a potential therapeutic target for asthma. The IL-7R is composed of an α-chain (CD127) and a β-chain (CD132) that is common to IL-2R family cytokines. Eosinophil expression of CD132 has been previously reported (28, 29). To
determine whether eosinophils express CD127, immunoblot analysis of highly purified blood eosinophils was performed in parallel with purified CD4\(^+\) T cells. A protein of \(70–80\) kDa was detected using a mAb specific for CD127 (Fig. 1A). CD127 was expressed on eosinophils from normal and allergic subjects. Densitometric analysis of the band detected in eosinophils from seven separate blood donors demonstrated that the level of CD127 is between 26% and 84% of the expression in an equal mass of a standard lymphocyte preparation (Fig. 1B). Because the non-eosinophil leukocyte contamination in our eosinophil preparations was 2% and the lysates from the eosinophil and T cell preparations yielded comparable protein mass per million cells (80 \(\mu\)g of protein per million cells for the T cell preparation vs 35–90 \(\mu\)g of protein per million cells for the seven eosinophil lysate donors), the immunoblot signal in the eosinophil lanes is not attributable to T cell contamination of the eosinophil preparations. It should also be noted that the immunoblot density of CD127 in the eosinophil preparations (Fig. 1B) does not correlate with the proportion of contaminating leukocytes.

**FIGURE 1.** Evidence of IL-7 receptor expression on human eosinophils. A, Representative immunoblot analysis for CD127 in cell lysates from highly purified (>99%) eosinophils (Eos) or CD4\(^+\) T lymphocytes (CD4) immunoblotted with either a mAb specific to CD127 (left) or an isotype control IgG1 (right). B, CD127 expression was analyzed by immunoblotting of 30 \(\mu\)g of cell lysate protein from seven separate eosinophil donors and quantified by densitometry. For each donor, the immunoblot density is summarized as a percentage of CD127 signal from 30 \(\mu\)g of the positive control T lymphocyte cell lysate run on the same gel and immunoblot.

**FIGURE 2.** Effect of IL-7 on survival of human eosinophils. A, Eosinophil survival in the presence of increasing concentrations of IL-7 or 300 pM GM-CSF. The number of viable eosinophils at 48 h was determined by trypan blue exclusion and expressed as a percentage of the number of cells at 0 h. *, \(p < 0.05\) (\(n = 7\) donors). B, Effect of GM-CSF neutralization on IL-7-induced eosinophil survival (\(n = 3\)). Eosinophils were preincubated for 1 h in the presence (■) or absence (□) of anti-GM-CSF (20 \(\mu\)g/ml) and then cultured for 48 h with medium, IL-7 (50 nM), or GM-CSF (300 pM).

**FIGURE 3.** Induction and kinetics of CD69 expression on eosinophils cultured with IL-7. A, Eosinophils were preincubated for 1 h with anti-GM-CSF (20 \(\mu\)g/ml, triangles) or an isotype control Ab (circles) and then cultured with medium (■), IL-7 (50 nM, filled symbols) or GM-CSF (300 pM, grayed symbols). Expression of CD69 was determined by flow cytometric analysis of eosinophils at 0, 0.5, 1, 3, 20, and 48 h. *, \(p < 0.05\) compared with 0 h; †, \(p < 0.05\) compared with treatment plus anti-GM-CSF (n = 4 donors). B, Effect GM-CSF neutralization on eosinophil morphology 48 h after culture with IL-7. Eosinophils were treated with IL-7 (50 nM), GM-CSF (300 pM), or medium in the presence of control Ab, or neutralizing Ab to GM-CSF (20 \(\mu\)g/ml).
back experiments in which PBMCs (3% of the total cell concentration) were cultured with highly purified (99.9%) eosinophils, there was no enhancement of IL-7-induced eosinophil survival (data not shown). Thus, the effect of IL-7 on eosinophil survival does not appear to be due to indirect production of GM-CSF by contaminating mononuclear cells.

**IL-7 promotes morphological changes in eosinophils and up-regulates CD69 through autocrine induction of GM-CSF**

CD69 is a marker of cell activation that is found on the cell surface within hours of eosinophil activation by a variety of stimuli including GM-CSF (34). CD69 was up-regulated by IL-7 within 1 h, peaked at 3 h, began to decrease within 20 h, but remained above background levels for at least 48 h (Fig. 3A). The kinetics and magnitude of IL-7-induced up-regulation of CD69 was similar to that induced by GM-CSF. Neutralization of GM-CSF completely abrogated IL-7-induced expression of CD69 at all time points (Fig. 3A). As additional evidence of their activation by IL-7, eosinophils were shown to undergo morphological changes that have been associated with cellular activation (35). Cells cultured in IL-7 or GM-CSF became flat and more amoeboid (Fig. 3B). In the presence of neutralizing Ab to GM-CSF, eosinophils maintained the spherical characteristics of cells cultured in medium (Fig. 3B). These data further support the notion that IL-7 induces autocrine release of GM-CSF by eosinophils. As with eosinophil viability, a role for contaminating monocytes was ruled out by demonstrating that addition of PBMCs (to 3% of the total cell concentration) to highly purified (99.9%) eosinophils had no effect on IL-7-induced expression of CD69 by eosinophils (data not shown).

**IL-7 induces activation of STAT5 through autocrine induction of GM-CSF**

In T cells, IL-7 is a potent activator of STAT5 (36). Likewise, in purified human eosinophils, IL-7 induced phosphorylation of STAT5 as determined by intracellular flow cytometric analysis (Fig. 4A). Addition of PBMCs (to 3% of the total cell concentration) to highly purified (99.9%) eosinophils had no effect on IL-7-induced phopsho-STAT5 in eosinophils (data not shown).

Using immunoblotting, an increase in phospho-STAT5 was detected within 10 min and persisted for at least 20 min (Fig. 4B). Furthermore, an upward shift in the mobility of the STAT5 band was seen, consistent with the observed phosphorylation (data not shown). STAT5 is also known to be activated by GM-CSF (24). Ab neutralization of GM-CSF diminished both GM-CSF- and IL-7-induced phosphorylation of STAT5 (Fig. 4B). Together the rapid kinetics of STAT5 phosphorylation stimulated by IL-7 and its neutralization by anti-GM-CSF, suggest that IL-7 stimulates autocrine production of GM-CSF from preformed intracellular stores. These data, coupled with data showing increased cellular activation and potentiation of eosinophil survival, suggest that both signaling processes and physiological endpoints in response to IL-7 occur as a result of GM-CSF released in an autocrine manner.

**Neutralization of IL-5 does not block IL-7-mediated activation of eosinophils**

IL-5 has previously been shown to mediate IL-7-induced eosinophil colony formation from human bone marrow cells (16). To determine...
whether autocrine release of IL-5 also contributes to IL-7-mediated activation of mature circulating eosinophils, cells were pretreated with neutralizing Ab to IL-5 before addition of IL-7. In contrast to neutralization of GM-CSF (Fig. 5, A and E), blocking IL-5 had no effect on IL-7-induced expression of CD69 (Fig. 5, B and E). The neutralizing Ab efficacy was confirmed (Fig. 5, C–E). Furthermore, based on analysis of propidium iodide exclusion/uptake by flow cytometric analysis, anti-IL-5 had no effect on IL-7-enhanced eosinophil viability after 48 h of culture. For example, in one experiment, the viability of eosinophils cultured for 48 h with IL-7 was reduced from 78% to 41% in the presence of neutralizing Ab to GM-CSF, but remained at 78% in the presence of anti-IL-5. The efficacy of the neutralizing Ab was confirmed by the observation that IL-5-induced viability was decreased from 83% to 22% in the presence of anti-IL-5. An identical pattern was observed for eosinophils from a different donor. Thus, in contrast to the effects of IL-7 on differentiation of eosinophil progenitors (16), the effect of IL-7 on survival and expression of CD69 on mature circulating eosinophils appears to be through autocrine induction of GM-CSF and not IL-5.

Concentrations of IL-7 increase in BAL fluid following airway allergen challenge and correlate with BAL eosinophil

To explore the potential in vivo relevance of IL-7 to allergen-induced eosinophilic airway inflammation, IL-7 levels were determined in BAL fluid obtained before and 48 h after segmental allergen challenge in subjects with allergic asthma. The total number of BAL cells increased from 36 ± 4 million at baseline (mean ± SEM) to 403 ± 72 million (p < 0.001) 48 h after SBP with allergen. The percentage of eosinophils increased from 2 ± 1% to 53 ± 4%. At baseline, IL-7 was detectable (>3 pg/ml) in 10X the concentrated BAL fluid from 12 of 18 subjects. Concentrations increased from 58 ± 37 pg/ml (mean ± SEM) at baseline to 236 ± 80 pg/ml 48 h after SBP with allergen (Fig. 6A). Notably, after allergen challenge, there was a statistically significant correlation determined by Spearman’s test (r_s = 0.71, p < 0.001) between IL-7 levels and the percentage of BAL eosinophils (Fig. 6B).

Discussion

We have established that highly purified human blood eosinophils express IL-7Rα (CD127) and that IL-7 stimulation of eosinophils leads to phosphorylation of STAT5. Moreover, we demonstrated a novel function of IL-7 for enhancement of human eosinophil survival and up-regulation of the activation marker CD69. An in vivo relevance for IL-7 was suggested by the observation that levels of IL-7 were highly correlated with eosinophils in BAL fluid of allergic asthma subjects 48 h after airway allergen challenge. These data suggest that IL-7 may play a role in allergen-induced eosinophilic airway inflammation that is associated with asthma.

The primary function of IL-7 is considered to be regulation of the development and survival of T cells; however, there have been sporadic reports that IL-7 can also affect nonlymphoid cells. For example, IL-7 has been shown to activate human monocyte tumoricidal activity and to induce their production of IL-6, IL-1, TNF-α and IL-8 (38, 39). Although a direct effect of IL-7 on mature eosinophils has not been previously reported, IL-7 has been shown to stimulate eosinophil colony formation from bone marrow cells (16). There is also indirect in vivo evidence associating eosinophils and IL-7. Eosinophils have long been noted in the thymus (38, 39), which is a principal location for IL-7 production. Although there is growing evidence that eosinophils can influence T cell function (19, 20), the significance of eosinophils at this T cell site remains a mystery. Eosinophil infiltrates have been reported in murine tumors engineered to overexpress IL-7 (40, 41) and in colonic mucosa of mice with selective overexpression of IL-7 in the colon (42). Conversely, eosinophils were lacking in a mouse model of colitis with targeted IL-7 deletion (43). Despite these scattered inferences to eosinophils and IL-7, to our knowledge this is the first report to demonstrate the IL-7Rα on eosinophils and to show their activation by IL-7.

Evidence that IL-7 can activate eosinophils included induction of STAT5 phosphorylation, stimulation of morphological changes consistent with cellular activation/migration, up-regulation of CD69 on the cell surface, and enhanced eosinophil survival. The effects of IL-7 were significantly reduced in the presence of blocking Abs to GM-CSF, but not anti-IL-5 suggesting that IL-7 activation of these particular eosinophil functions is mediated via autocrine production of GM-CSF. Neutralization of GM-CSF reduced STAT5 phosphorylation within 10 min of eosinophil exposure to IL-7. The rapid kinetics of the anti-GM-CSF-mediated effect raises the possibility that IL-7 can induce autocrine release of preformed GM-CSF. Indeed, there are reports that GM-CSF is stored in crystalloid granules of eosinophils (44). The kinetics of inhibition of GM-CSF activity is reminiscent of eosinophil storage and rapid release of preformed RANTES (45) and IL-4 (46), which are reported to be stored in specialized small secretory vesicles and selectively released by a process known as piece-meal degranulation (47, 48). Bandeira-Melo and colleagues (49) showed that eotaxin-induced IL-4 release could not be measured by ELISA, but was instead detected by a unique gel-based dual Ab detection assay. Thus, the fact that we were not able to directly detect GM-CSF production by eosinophils is not unexpected. A number of reports have demonstrated that eosinophil survival induced by factors such as IL-15 (33), hyaluronic acid (32), or TNF-α plus fibronectin (32) can be reversed by neutralization of GM-CSF, yet demonstrable levels of GM-CSF could not be measured by ELISA. Furthermore, it has been shown that the continuous presence of
minute amounts of GM-CSF is sufficient to inhibit eosinophil apoptosis (30).

We recognize that there are inherent limitations to our studies. First, nanomolar concentrations of IL-7 were necessary for activation of eosinophils. This observation is consistent with what has been reported for IL-7-induced release of GM-CSF by T cells (30). The reason why GM-CSF release by T cells and eosinophils requires relatively high concentrations of IL-7 is not known. There is evidence that human T cells express both high and low affinity IL-7 receptors (51). It is possible that IL-7-induced GM-CSF release occurs through activation of low affinity receptors, and thus requires higher concentrations of IL-7 to achieve effective cell signaling and functional cellular responses. The report that IL-7 can stimulate GM-CSF production by T cells (50) raises a second potential limitation. It is possible that the small numbers of T cells or other mononuclear cells present in our eosinophils preparations (generally <2%) contribute to the effects of IL-7 on eosinophils. This scenario is unlikely based on our observation that an eosinophil preparation of 99.9% purity responded to IL-7 and addition of 3% PBMC did not further enhance IL-7-induced eosinophil survival, expression of CD69 or levels of STAT5 phosphorylation. Finally, although we have clearly demonstrated the presence of CD127 mRNA expression (17) and the protein by Western blot analysis (Fig. 1), the detectable level of the receptor by flow cytometric analysis is low and inconsistent. The fact IL-7Rα is detected by immunoblotting at levels between 26% and 84% of the expression in an equal mass of a standard lymphocyte preparation and that eosinophils respond to stimulation with IL-7 with respect to multiple biological readouts, is consistent with an IL-7R conformation in eosinophils that limits binding or accessibility of the mAbs used for flow cytometry. We suspect that in eosinophils, the receptors may be sequestered in multiprotein complexes, caveolae or in other cellular microdomains that mask the epitope detected by the mAb used for flow cytometric analysis.

In concert with our in vitro studies demonstrating a direct effect of IL-7 on eosinophils, we have also shown that airway eosinophilia induced by allergen challenge of allergic asthma subjects is associated with increased BAL fluid concentrations of IL-7. The source of IL-7 in BAL fluid was not determined in this study. Epithelial cells are the principal source of IL-7 in tissues where IL-7 is predominant including the thymus, bone marrow, and intestine (12). Although there is a paucity of studies on IL-7 in the airway, there is some evidence that BAL cells express IL-7. An early report documented IL-7 mRNA in BAL cells from lung transplant patients (52) and a more recent study demonstrated IL-7 staining of alveolar macrophages and epithelial cells in cytospin preparations of BAL cells from patients with concurrent infection with HIV-associated tuberculosis (53). Further studies of BAL cells and bronchial biopsy studies are required to determine the source of IL-7 in the airway of asthma subjects following allergen challenge. There is also a need to determine whether these cells are directly activated by allergen or indirectly affected by factors produced by other IL-7-responsive cells such as T cells and monocytes. For example, IL-7 synthesis by epithelial cells can be up-regulated by INF-γ, IL-1, or TNF-α (54, 55).

The presence of IL-7 adds to the redundancy of eosinophil survival factors in the airway after allergen exposure. In asthma, one could envision that IL-7 may provide a pathway for GM-CSF production and enhanced survival of eosinophils in the event of deficient production by prominent GM-CSF-producing cells such as airway epithelial cells and/or alveolar macrophages. Furthermore, the ability of IL-7 to promote eosinophil survival and induce the eosinophil survival factor GM-CSF may contribute to eosinophilia in nonatopic airway diseases that are not typically associated with increased levels of the eosinophil-specific cytokine IL-5.

In summary, we have established a novel function for IL-7 in the activation of eosinophils and potentiation of their survival, and have demonstrated that levels of IL-7 in BAL fluid are increased by airway allergen challenge and parallel the influx of eosinophils, thus supporting the notion that IL-7 contributes to airway inflammation by promoting eosinophil activation and survival.

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Disclosures
The authors have no financial conflict of interest.

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