The interaction of human peripheral blood eosinophils with bacterial lipopolysaccharide is CD14 dependent

Sabine G. Plötz, Arnd Lentschat, Heidrun Behrendt, Werner Plötz, Lutz Hamann, Johannes Ring, Ernst Th. Rietschel, Hans-Dieter Flad, and Artur J. Ulmer

Bacterial lipopolysaccharide (LPS, endotoxin) is a ubiquitous component of dust and air pollution and is suspected to contribute after inhalation to an activation of eosinophils in bronchial tissues of asthmatic patients, provoking inflammatory and allergic processes. We were therefore interested in the interaction of eosinophil granulocytes with LPS and have examined the activation of and uptake to human peripheral blood eosinophils by LPS. Eosinophils were stimulated by LPS and the endotoxic component lipid A and the release of tumor necrosis factor alpha (TNF-α) and of the eosinophil-specific granule protein eosinophil cationic protein (ECP) was estimated. The results show induction of TNF-α and ECP-release by LPS and lipid A in a dose-dependent manner. Anti-CD14 monoclonal antibody (moAb) (clone MEM-18) and the synthetic lipid A partial structure 406 blocked the release of TNF-α and ECP by LPS-stimulated eosinophils. Studies with radioactively labeled LPS showed dose-dependent uptake of 3H-LPS to eosinophils. The 3H-LPS uptake was found to be specific because preincubation with unlabeled LPS, compound 406 and also anti-CD14 antibodies inhibited uptake of 3H-LPS to eosinophil granulocytes. By flow cytometry using anti-CD14 moAb and by reverse transcriptase-polymerase chain reaction (RT-PCR) technique, CD14 expression was detectable. Furthermore, messenger RNA (mRNA) expression of Toll-like receptors (TLR) 2 and TLR 4 was detected, indicating the presence of these CD14 coreceptors. The results indicate that eosinophils can take up LPS and can be stimulated by LPS in a CD14-dependent manner. Hence, in addition to allergens, eosinophils interact with endotoxin, a process that possibly exacerbates ongoing inflammatory and allergic processes. (Blood. 2001;97:235-241)

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Introduction

Human eosinophils, like other granulocytes, are terminally differentiated effector cells that are recruited from the bloodstream into tissue sites during inflammatory, particularly allergic, reactions.1 In asthmatic patients, the airways contain an increased number of eosinophils and the severity of their asthmatic symptoms correlates with the number of eosinophils in the bronchial tissue.2-4 Eosinophils synthesize and release a number of substances, including leukotrienes, and a variety of granule-associated proteins such as eosinophil cationic protein (ECP). If released inappropriately, these substances contribute to tissue damage and to the pathogenesis of allergic diseases.1,4 In addition to their capacity to release lipid mediators and cytototoxic granule proteins, eosinophils may contribute to the inflammatory process through expression and synthesis of cytokines including tumor necrosis factor alpha/beta (TNF-α/β), macrophage inflammatory protein 1 alpha (MIP-1α), interleukin-1 (IL-1), IL-5, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6, IL-8, and TNF-α. Furthermore, cytokines increase expression of β2 integrins on eosinophils, which are involved in the adhesion, transendothelial migration of eosinophils, and also in a variety of adherence-dependent functions.5,7

Although stimuli such as calcium ionophore and ionomycin have been found capable of eliciting cytokine expression in eosinophils in vitro,5,9 physiologic stimuli and the mechanisms that are involved in the regulation of eosinophil cytokine responses remain largely unknown. A potent candidate stimulus is lipopolysaccharide (LPS, endotoxin), the major constituent of the outer membrane of gram-negative bacteria.10 LPS is present in the upper respiratory tract,11 and its levels increase in the infected and inflamed state locally and systemically. Furthermore, LPS is a continuous ingredient of the environment, including air pollution.12,13 In this context, LPS has been detected in a variety of dust extracts, and it has been suggested that chronically inhaled airborne endotoxin could contribute to the development or the enhancement of several chronic obstructive bronchial diseases, including asthma.12,14-19 Inhalation of low doses of endotoxins has been reported to contribute to bronchial constriction in asthmatic patients.16-18 Hence, in addition to allergens, LPS inhalation could further activate myeloic cells, including eosinophils, thus exacerbating the ongoing inflammatory process.

To our knowledge, the only evidence for stimulation of human eosinophils by LPS has been provided by the work of Takanashi et al,20 showing release of GM-CSF, TNF-α, and IL-8 in LPS-stimulated human peripheral blood eosinophils. However, the mechanism underlying interaction of LPS with eosinophils was not investigated. In monocytes/macrophages as well as in neutrophils, it is accepted that LPS binds to a specific membrane receptor, the...
55-kd, glycosylphosphatidylinositol (GPI)-anchored, membrane-bound CD14 molecule\(^{21-26}\) that is also present as a soluble protein (sCD14) in serum.\(^{27}\) CD14 binds lipid A, the endotoxic principle of strain LCD25.\(^{34}\) This preparation was obtained from LIST Biological globulin IgG1\(^{2}\) and was a kind gift from V. Horejsi (Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Republic). The CD14-specific moAb used was MEM-18 (Immuno-Diagnostic Systems, Neuss, Germany), Serva (Heidelberg, Germany), or Pharmingen (Becton Dickinson, Heidelberg, Germany). Unless otherwise indicated, all fine chemicals were purchased from Sigma (St. Louis, MO).

In this report, we demonstrate that the inflammatory agent LPS and its endotoxic principle lipid A are activators of secretion of both the inflammatory cytokine TNF-\(\alpha\) and the eosinophil-specific granule protein ECP. Moreover, for the first time we demonstrate that eosinophils do take up LPS in a specific way. Our data show that CD14 indeed appears to be involved in eosinophil activation and LPS uptake, thus providing potential novel mechanisms for activation and regulation of functions of human eosinophils. Moreover, expression of the recently discovered LPS coreceptors Toll-like receptors (TLR) 2 and TLR4, which may be responsible for transmembrane signaling induced by LPS,\(^{29,30}\) were detected in human peripheral blood eosinophils.

### Materials and methods

#### Lipopolysaccharide, lipid A, and lipid A partial structure

LPS was prepared from *Salmonella* friedens to be purified by the phenol-chloroform-petroleum ether method.\(^{31,32}\) This preparation contains less than 0.2% protein and nucleic acid as determined by chemical analysis. Lipid A was obtained from the *Escherichia coli* Re-mutant strain F515 by treating phenol-chloroform-petroleum ether-extracted LPS with acetate buffer.\(^{32}\) LPS as well as lipid A was kindly provided by H. Brade (Research Center Borstel, Borstel, Germany). Synthetic compound 406 (precursor I), which represents a tetraacyl partial structure of *E. coli* lipid A lacking dodecanedioic and tetradecanoic acids, was synthesized as described previously.\(^{33}\) Compound 406 was a kind gift of S. Kusumoto (Osaka University, Osaka, Japan).

\(^{3}\)H-LPS was biosynthetic radiolabeled and isolated from the *E. coli* K-12 strain LCD25.\(^{34}\) This preparation was obtained from LIST Biological Laboratories, Campbell.

#### Reagents and antibodies

Unless otherwise indicated, all fine chemicals were purchased from Sigma (Deisenhofen, Germany), Serva (Heidelberg, Germany), or Pharmingen (San Diego, CA). The CD14-specific moAb used was MEM-18 (Immuno-globulin IgG1)\(^{2}\) and was a kind gift from V. Horejsi (Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Republic); purified mouse IgG1 (Sigma) was used as the isotype control. Normal human sera were obtained from healthy volunteers.

### Eosinophil isolation

Blood was drawn from healthy nonatopic volunteers and separated by density gradient centrifugation with Ficoll-Isopaque (Pharmacia, Freiburg, Germany). The bottom layer containing neutrophils, eosinophils, and erythrocytes was harvested and analyzed for cytokine activity or ECP content. The concentration of at least 500 cells to ensure pure eosinophil preparation. The count of at least 500 cells to ensure pure eosinophil preparation.

### Isolation of peripheral blood mononuclear cells and monocytes

Peripheral blood mononuclear cells (PBMCs) from healthy donors were obtained from the top layer after density gradient centrifugation on Ficoll-Isopaque (Pharmacia). After repeated washing in HBSS (Biochem, Berlin, Germany), monocytes were isolated by counterflow elutriation using the JE-6B elutriator system (Beckmann Instruments, Palo Alto, CA) as described previously.\(^{15}\)

### TNF-\(\alpha\) and eosinophil cationic protein release in human eosinophils

Cell cultures were prepared in RPMI 1640 medium (Biochem) supplemented with 10% human serum, 100 U/mL penicillin, and 100 \(\mu\)g/mL streptomycin. For the stimulation experiments, eosinophils (2 \(\times\) 10\(^6\)/mL) were treated with LPS or lipid A for 16 hours at 37°C (under 5% CO\(_2\)) in 200-\(\mu\)L cultures (triplicate wells) in U-form microtiter plates (Greiner, Nürtigen, Germany). For inhibition studies, anti-CD14 moAb (MEM-18) or the antagonistic compound 406 was added at 4°C to the cells for 20 minutes before stimulation with LPS or lipid A. After incubation, supernatants were harvested and analyzed for cytokine activity or ECP content. The concentration of TNF-\(\alpha\) in supernatants was determined by enzyme-linked immunosorbent assay (ELISA). ECP content in supernatants was measured with the RIA kit (Pharmacia) as described by the manufacturer.

### Uptake of \(^{3}\)H-LPS

For determination of \(^{3}\)H-LPS uptake, eosinophils, PBMCs, or monocytes were seeded in 24-well plates (2 \(\times\) 10\(^3\) cells/mL). Incubation with \(^{3}\)H-LPS was performed in the presence of 10% human serum for 1 hour at 37°C, cells were washed 3 times with PBS and lysed in PBS containing 2% SDS. Tritium counting of the lysates was performed in a liquid scintillation counter (Packard). In blocking experiments, eosinophils were pretreated with anti-CD14 moAb (MEM-18), the isotype control IgG1 (Sigma), the antagonistic compound 406, or unlabeled LPS for 30 minutes.

### Flow cytometry

Flow cytometric analysis were performed using a FACScan Calibur (Becton Dickinson, Heidelberg, Germany). For immunofluorescent staining, anti-CD14–FITC moAb (Miy-4-FITC; IgG2b) from Coulter were used. The cells (10\(^6\)/mL) were washed, resuspended in 100 \(\mu\)L of azide-PBS and incubated with the FITC-labeled anti-CD14 antibodies for 30 minutes at 4°C. Incubation was stopped by adding 1.5 mL ice-cold azide-PBS. After washing, the cells were resuspended in 400 \(\mu\)L azide-PBS. Unlabeled cells and cells incubated with the isotype (IgG2b-FITC, Sigma) were used as controls.

### Reverse transcriptase-polymerase chain reaction

Eosinophil and monocyte messenger RNA (mRNA) was isolated from 2 \(\times\) 10\(^5\) cells using oligo-dT magnetic beads (Dynal, Hamburg, Germany), according to the manufacturer’s instructions. Synthesis of complementary DNA (cDNA) was performed with Oligo-dT\(_\text{17}\) as the primer for reverse transcriptase (Superscript, Gibco-BRL, Eggenstein, Germany) in the presence of 650 U/mL RNase-inhibitor. Thirty cycles of amplification of cDNA was conducted in an automatic DNA thermal cycler (Perkin-Elmer Cetus, Norwalk, CT) using an annealing temperature of 52°C (hCD14) or 58°C (hTLR2 and hTLR4). For the amplification of 2 \(\mu\)L cDNA, 200 \(\mu\)M deoxynucleotide triphosphate (Pharmacia), 1.25 units Taq polymerase (Gibco-BRL), and gene-specific sense and antisense primers (1 \(\mu\)M for hCD14, 1 hTLR2, and hTLR4; or 0.1 \(\mu\)M for \(\beta\)-actin) were used at a final volume of 50 \(\mu\)L. PCR primer used were for hCD14 (ACTTA TCGACCA T- Bgl II, Boehringer, Mannheim, Germany) were resolved

For inhibition studies, anti-CD14 moAb (MEM-18) or the antagonistic compound 406, or unlabeled LPS for 30 minutes.
by 1.5% agarose gel electrophoresis, and DNA bands were visualized by staining the gel with 0.01 mg/mL ethidium bromide.

Statistics

Each experiment was performed at least 3 times with cells from different donors. From these experiments, a typical one is shown demonstrating representative results. The results represent the mean ± SD of triplicate cultures. P values, if demonstrated, are estimated by the Student t test.

Results

LPS and lipid A–induced cytokine production in eosinophils

First, we investigated the ability of LPS and lipid A to induce the cytokine TNF-α. Eosinophils (2 × 10^6/mL) were stimulated with increasing concentrations of LPS (A and C) or lipid A (B and D) as indicated for 16 hours. TNF-α content in the culture supernatant was measured by ELISA (A and B). ECP concentration was determined in radioimmunoassay (C and D).

Effect of anti-CD14 moAb and lipid A partial structures on LPS-induced cytokine release by eosinophils

To find out whether the LPS-induced TNF-α release by human eosinophils was CD14 dependent, eosinophils (2 × 10^6/mL) were preincubated in the presence of various concentrations of anti-CD14 moAb (MEM-18) for 20 minutes at 4°C. In addition, the use of compound 406, a synthetic antagonistic lipid A partial structure, showed that interaction of LPS with eosinophils is similar to that found in monocytes and neutrophils. After 16 hours of stimulation with LPS (100 ng/mL), supernatants were harvested and the TNF-α content was determined by ELISA. Whereas the anti-CD14 moAb or compound 406 alone was not able to induce TNF-α production in eosinophils, both reagents inhibited LPS-induced release of TNF-α (Figure 2A,B). Mouse IgG1, which was used as an isotype control, could not reduce the LPS-induced monokine production.

Effect of anti-CD14 moAb and lipid A partial structures on LPS-induced release of ECP in eosinophils

This experiment was performed to prove whether the LPS-induced ECP release was also CD14 dependent. To answer this question, eosinophils (2 × 10^6/mL) were preincubated in the presence of various concentrations of the anti-CD14 moAb (MEM-18) or the lipid A partial structure compound 406 for 20 minutes at 4°C. After 16 hours of stimulation with LPS (100 ng/mL), supernatants were harvested, and ECP content was determined by RIA. The anti-CD14 moAb or compound 406 alone was not able to induce ECP production in eosinophils. The results show that anti-CD14 moAb and compound 406 both blocked the LPS-induced release of ECP (Figure 2A,B). Mouse IgG1, which was used as an isotype control, could not reduce the LPS-induced ECP production.

Figure 1. Induction of TNF-α and ECP release in human eosinophils by LPS and lipid A. Eosinophils (2 × 10^6/mL) were stimulated with increasing concentrations of LPS (A and C) or lipid A (B and D) as indicated for 16 hours. TNF-α content in the culture supernatant was measured by ELISA (A and B). ECP concentration was determined in radioimmunoassay (C and D).

Figure 2. Inhibition of LPS-induced TNF-α and ECP release by anti-CD14 mAb and compound 406. Eosinophils were preincubated with increasing concentrations of anti-CD14 mAb MEM-18 (A and C) and the antagonistic compound 406 (B and D) for 20 minutes at 4°C. After 16 hours of stimulation with LPS (100 ng/mL), supernatants were harvested. TNF-α content in the culture supernatant was measured by ELISA (A and B). ECP concentration was determined in radioimmunoassay (C and D).
Specific ³H-LPS uptake by human eosinophils

In further studies, we compared the uptake of ³H-LPS by eosinophils, mononuclear cells, and monocytes. It was found that all cells showed dose-dependent uptake of ³H-LPS. However, the ³H-LPS uptake of monocytes and mononuclear cells was considerably higher than the ³H-LPS uptake of eosinophils (Figure 3). A statistical significant (P ≤ 0.05) uptake of ³H-LPS by eosinophils was observed with 100 ng/mL or more.

Next, we analyzed the specificity of ³H-LPS uptake by human eosinophils by using unlabeled LPS. For further characterization of the structural requirement of ³H-LPS uptake of eosinophils, we also investigated the inhibiting activity of anti-CD14 mAb and compound 406 in this system. Cells were pretreated with unlabeled LPS, compound 406 (Figure 4A), or with anti-CD14 mAb (MEM-18) (Figure 4B) for 30 minutes, followed by an incubation with ³H-LPS. The specificity of the uptake of ³H-LPS could be confirmed by the addition of unlabeled LPS in eosinophils as well as in PBMCs and monocytes (Figure 4A). In addition, compound 406 and anti-CD14 mAb also led to a drastic decrease of ³H-LPS uptake in eosinophils (Figure 4A,B). No effect on ³H-LPS uptake of eosinophils was observed after preincubation with an isotype mAb, IgG1 (Figure 4B).

Expression of CD14 on human eosinophils

Inhibition of LPS-stimulation and ³H-LPS uptake in human eosinophils by anti-CD14 mAb indicated the presence of CD14 on the surface of these cells. Proof for the expression of this membrane molecule was obtained by anti-CD14 mAb and flow cytometric analysis. The results of these experiments showed an expression of CD14 on eosinophils to a degree less than that found on neutrophils (Figure 5). However, it should be mentioned that, in 2 of the 10 experiments, a similar degree of CD14 expression on eosinophils and neutrophils was found (data not given).

We also used RT-PCR and detected CD14-mRNA expression on human eosinophils (Figure 6A). Because the eosinophil preparations that we used were highly purified (more than 98%), the possibility that mRNA expression was due to other cells types such as monocytes seems very unlikely. To completely rule out this option, a preparation containing the maximum number of potentially contaminating monocytes (1:20) was investigated for CD14 mRNA expression. Although CD14 mRNA was also detectable by RT-PCR with this low number of monocytes, much smaller amounts of RT-PCR products were detected from these cells, indicating that the contribution of monocytes to the CD14 mRNA expression in eosinophils was indeed negligible (Figure 6A).
Expression of TLR2 and TLR4 on human eosinophils

TLR2 and TLR4 are transmembrane molecules recently described to be CD14 coreceptors during LPS stimulation. Here we used RT-PCR to investigate the expression of these molecules in human eosinophils. The data show the presence of TLR2 and TLR4 mRNA in human peripheral blood eosinophils (Figure 6B).

Discussion

LPS is known to trigger release of cytokines in monocytes and neutrophils,10,22,24,26,37 and endotoxin-induced leukocyte infiltration has been widely studied. However, the interaction between eosinophils and microbial components such as LPS so far has not been defined in detail. In an attempt to better understand the relationship between LPS and eosinophils, it was of interest therefore to determine whether eosinophils directly interact with or respond to LPS.

Our data show that LPS induces the release of TNF-α of human eosinophils (Figure 1A). This is consistent with the findings of Takahashi et al.20 These authors have stimulated isolated eosinophils in the presence of LPS and found expression of TNF-α, GM-CSF, and IL-8. Expression of ECP induced by LPS stimulation has not been investigated so far but is evident from the results presented in Figure 1C,D. Cellular content of ECP in normal eosinophils has been measured to be about 10 μg/10⁶ cells.4 Therefore, from our results, we calculate that LPS-stimulated eosinophils release up to 10% of the total available pool of ECP.

Our special interest focused on the question whether this activation is CD14 dependent, and whether it can be inhibited by antagonistic lipid A partial structures. Our data show that CD14 indeed appears to be involved in eosinophil activation by LPS (Figure 2A,C). Furthermore, the current study demonstrates a CD14-dependent uptake of LPS to human eosinophils (Figure 3). The involvement of CD14 is evident in FACS analyses (Figure 5) as well as in experiments showing the blocking of activation and ³H-LPS uptake of the cells by anti-CD14 moAb (Figure 4B).

The ³H-LPS uptake was found to be dose dependent and specific, as the addition of a 10-fold excess of unlabeled LPS resulted in a nearly complete inhibition of the ³H-LPS uptake (Figure 4A). From our results, we have calculated uptake of 60 pg ³H-LPS/10⁶ cells or 9000 molecules per cell after incubation of the eosinophils with 20 ng ³H-LPS/mL. This rate is at the low range of the amount of LPS-uptake found in neutrophils.37 Concerning the role of CD14 as a site of LPS recognition, our experiments show that this protein is involved. First, anti-CD14 moAb (clone MEM-18), which blocks the biologic activity of LPS, as well as the uptake to human monocytes and neutrophils, also inhibits the specific uptake of LPS to human eosinophils (Figure 2A,C). Second, the same inhibition was also observed by the use of compound 406, a lipid A partial structure (Figure 2B,C). Compound 406 has been said to represent an LPS antagonist that inhibits LPS bioactivity28,38,39,40 and, in higher doses, effectively blocks the uptake of LPS in a competitive way.41 At low doses, a noncompetitive inhibition by compound 406 has been shown in THP-1 cells.42

The presence of CD14 on eosinophils has been demonstrated by flow cytometric analysis (surface CD14) as well as by RT-PCR (CD14 mRNA) (Figures 5 and 6A). It has been previously mentioned, however, that eosinophils isolated from nonatopic healthy donors did not express CD14 molecules on their surfaces.20 The eosinophils used in those experiments were of the same sources and were isolated by a method similar to that used in our experiments. In contrast to our examinations, however, the expression of CD14 was investigated by an immunocytochemical method, which was not described in detail. Thereby, the immunocytochemical method and the type of antibody used in those experiments was not described by the authors.20 The reasons for these conflicting data are therefore not obvious. However, the amount of CD14 expressed by eosinophils is rather low, and therefore we like to speculate that the lower sensitivity of the immunocytochemical method or of the anti-CD14 moAb used may account for the failure of detection of CD14.

Most recently, members of the human TLR2 and TLR4 have been implicated in the responses of cells to LPS. Toll is a type I transmembrane receptor that was first identified in Drosophila melanogaster for its role in larval development.43 At least 6 mammalian TLRs have recently been described.44,45 TLRs were proposed as candidates for the CD14-associated transmembrane signal transduction. Thus, transfection of human TLR2 into HEK 293 cells rendered these otherwise LPS nonresponsive cells responsive to LPS.29,30 TLR4 was proposed as a candidate for its role in larval development.43 At least 6 TLR2, and TLR4 (B) on human eosinophils and monocytes. Eos: Eosinophils (2 × 10⁶ cells); Mo: monocytes (2 × 10⁶ cells); Monocytes 1:20: monocytes 1:20; monocytes (0.1 × 10⁶ cells); N: negative control without mRNA; M: molecular weight markers.

Figure 6. CD14, TLR2, and TLR4 mRNA expression of eosinophils and monocytes. RT-PCR was performed to analyze the mRNA expression of CD14 (A), TLR2, and TLR4 (B) on human eosinophils and monocytes. Eos: Eosinophils (2 × 10⁶ cells); Mo: monocytes (2 × 10⁶ cells); Monocytes 1:20: monocytes (0.1 × 10⁶ cells); N: negative control without mRNA; M: molecular weight markers.
human eosinophils with these further potential LPS-binding sites remains to be elucidated.

In summary, our data provide evidence that the inflammatory agent LPS and its endotoxic principle lipid A are activators of secretion of both the inflammatory cytokine TNF-α and the granule protein ECP in human eosinophils. Moreover, we demonstrate that eosinophils do take up LPS in a specific way and that anti-CD14 mAbs and compound 406 are also potent inhibitors of uptake and activation induced by LPS. Our data thus provide potential novel mechanisms for activation and regulation of functions of human eosinophils that may lead to a better understanding of inflammatory response, eg, in chronic obstructive bronchial diseases, including asthma.

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This paper is dedicated to our dear friend and estimated colleague Prof Dr Shiochi Kusumoto, University of Osaka, Japan, on the occasion of his 60th birthday.

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7. Neeley S-P, Hamann K-J, White S-R, Baranowski J, Kamping F-P. Endotoxin-induced inflammation and the granule protein ECP in human eosinophils. Moreover, we demonstrate that eosinophils do take up LPS in a specific way and that anti-CD14 mAbs and compound 406 are also potent inhibitors of uptake and activation induced by LPS. Our data thus provide potential novel mechanisms for activation and regulation of functions of human eosinophils that may lead to a better understanding of inflammatory response, eg, in chronic obstructive bronchial diseases, including asthma.

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