The C-C Chemokine Receptor CCR3 Participates in Stimulation of Eosinophil Arrest on Inflammatory Endothelium in Shear Flow

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Abstract

Chemokines are widely hypothesized to stimulate firm adhesion of leukocytes on endothelium in shear flow. Thus far, this has been demonstrated experimentally for exogenously added chemoattractants, but not for those released by endothelium. We found that human umbilical cord endothelial cells (HUVEC) stimulated with TNF-α and IFN-γ secreted eosinophil chemoattractants into the culture supernatant. This material induced transendothelial chemotaxis, stimulated eosinophil binding to purified intercellular adhesion molecule 1, and augmented binding to purified vascular cell adhesion molecule 1 in a 3-min static assay. Chemotaxis and stimulation of adhesion were abrogated completely by the pretreatment of eosinophils with an mAb to the C-C chemokine receptor 3 (CCR3). Eosinophils accumulated efficiently on HUVEC stimulated with TNF-α and IFN-γ in shear flow at 1.5 dyn/cm². CCR3 mAb slightly but significantly reduced eosinophil arrest and accumulation, by preventing development of firm adhesion by some of the tethered eosinophils, so that they detached within 30 s after the initial tethering. In the presence of mAb to the α4 integrin subunit, the effect of CCR3 mAb was more prominent, and approximately half of eosinophil arrest and accumulation was abolished. Inhibition by CCR3 mAb in the presence of β2 integrin mAb was similar to that in control eosinophils. This is the first evidence that endothelial cell–derived chemokines can activate firm adhesion through α4 and β2 integrins even in the presence of shear flow. (J. Clin. Invest. 1998. 101:2017–2024.) Key words: endothelium • eosinophils • chemokine receptor • very late antigen 4

Introduction

Leukocyte emigration into inflammatory sites is a multistep process mediated by a series of sequential but partially overlapping interactions (1, 2). Tethering and rolling on endothelium are followed by development of firm adhesion, i.e., arrest, and then by diapedesis. It is generally accepted that rolling leukocytes encounter factors that stimulate upregulation of integrin-dependent adhesion, which is required for arrest and transmigration. Although the exact mechanisms are not clearly understood, chemoattractants locally produced from endothelial or stromal cells have been proposed as a possible mechanism to activate the rolling leukocytes and upregulate integrin function. In flow assays with neutrophils or transfectants, it has been shown that FMLP (3, 4) and IL-8 (5) can enhance integrin-mediated adhesion to intercellular adhesion molecule (ICAM)1 or vascular cell adhesion molecule (VCAM) 1. However, in those studies, the chemoattractants were added exogenously. In vivo, chemoattractants released from the luminal surface of the endothelium would be rapidly diluted and swept downstream by blood flow, and the concentration of chemoattractants that flowing or rolling leukocytes actually encounter may be much lower than when chemokine is added exogenously. Although some chemoattractants have been reported to be retained on the endothelial surface (6), and a chemokine bound to a leukocyte-derived, purified proteoglycan, CD44, can augment leukocyte adhesion in stasis (7), it is still unclear whether membrane-associated chemoattractants can actually stimulate integrin avidity in flow. Eosinophils often predominate in tissues with chronic allergic inflammation, such as reactive airways, allergic rhinitis, or atopic skin reactions (8, 9). In contrast to neutrophils that are stimulated mainly by CXC chemokines such as IL-8 and Gro proteins, eosinophils show chemotaxis and Ca²⁺ influx responses to C-C chemokines, including RANTES (for regulated upon activation, normal T cell expressed and secreted) (10–12), macrophage inflammatory protein 1α (11), monocyte chemotactic protein (MCP) 2 (13), MCP-3 (14), MCP-4 (15), and eotaxin (16–20). On eosinophils, RANTES and MCP-3 stimulate transient α4β1 integrin and prolonged β2 integrin avidity in stasis (21). Information on the receptors for chemokines is growing rapidly. Many different G protein–coupled receptors for C-C chemokines and for CXC chemokines have been molecularly characterized (22, 23). Mononuclear cells express and respond to multiple chemokine receptors (23–25). Eosinophils but not resting mononuclear cells or neutrophils express the C-C chemokine receptor (CCR) 3 (26–28). Furthermore, CCR3 appears to be the predominant chemokine receptor on non-mesenchymal eosinophils. An mAb to CCR3, 7B11, can inhibit completely eosinophil chemotaxis to RANTES, MCP-2, MCP-3, MCP-4, and eotaxin (28). Using this mAb, we have examined the role of endothelial cell–derived chemokines on eosinophil accumulation and arrest on activated endothelial cells with an in vitro laminar flow assay.

1. Abbreviations used in this paper: CCR, C-C chemokine receptor; CTx, cholina toxin; HUVEC, human umbilical cord endothelial cell(s); ICAM, intercellular adhesion molecule; MCP, monocyte chemotactic protein; PAF, platelet-activating factor; PTx, pertussis toxin; RANTES, regulated upon activation, normal T cell expressed and secreted; VCAM, vascular cell adhesion molecule.

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Methods

Reagents and antibodies. Recombinant TNF-α, IFN-γ, and IL-4 were purchased from Genzyme Corp. (Cambridge, MA). mAbs 7B11 to CCR3, and 7D9 to IL-8RA (both mlgG1) were characterized previously (28, 29). mAbs HP2/1 to integrin α4 (Amac, Inc., Westbrook, ME) and TS1/18 to integrin β2 (30) were used as purified IgG. ICAM-1 was immunopurified on an R6.5 mAb-Sepharose column (31), and the soluble form of VCAM-1 (32) was a generous gift from Dr. R. Lobb (Biogen, Inc., Cambridge, MA). For blocking experiments, the mAbs were added to 106 cells suspended in 0.1 ml HBBS with 10 mM Hepes, pH 7.4, at a final concentration of 20 μg/ml for each mAb. After 1 h incubation on ice, the cells were diluted to 1.0 ml of assay medium (10% heat-inactivated FCS plus RPMI 1640) for transmigration and static adhesion assay; HBSS with 10 mM Hepes including 2 mM Ca2+, 1 mM Mg2+, and 10% FCS, pH 7.4, for flow assay) and used for experiments. Pertussis toxin (PTx) and cholera toxin (CTx) were purchased from Calbiochem Corp. (San Diego, CA), and UK-74505 was a gift from Pfizer Ltd. (Sandwich, Kent, UK). Eosinophils were treated with these reagents as described for mAb above.

Cell purification. Eosinophils were purified from healthy volunteers by negative immunomagnetic selection (33). Briefly, granulocytes were isolated from citrate-anticoagulated whole blood by dextran sedimentation, Ficoll-Hypaque centrifugation, and hypotonic lysis of red blood cells. The cells were washed twice with PBS with 1% BSA and 5 mM EDTA, and incubated with anti-CD16-conjugated microbeads (MACS; Miltenyi Biotec Inc., Sunnyvale, CA) for 30 min on ice. The cell suspensions were then applied onto a magnetic column (MACS column), and negative populations were collected. The isolates routinely contained > 99% eosinophils with viability > 95% by Trypan blue exclusion.

Preparation of human umbilical vein endothelial cell (HUVEC) monolayer. HUVEC were isolated and cultured in flasks coated with 25 μg/ml fibronectin (Sigma Chemical Co., St. Louis, MO) with medium 199 (M199) supplemented with 15% FCS (Sigma Chemical Co.), 50 μg/ml endothelial mitogen (Biomedical Technologies, Inc., Stoughton, MA), and 100 μg/ml heparin (Sigma Chemical Co.) (34). Primary or first passage HUVEC were used for all experiments.

Transmigration assay. Confluent HUVEC were cultured in endothelial culture medium with or without optimal concentrations of IL-4 (10 ng/ml), TNF-α (100 U/ml), and/or IFN-γ (100 U/ml) for 22 h, then the monolayers were washed with RPMI 1640 three times and incubated in 1 ml of 10% FCS plus RPMI 1640 for another 2 h. The supernatants were collected and kept at −20°C until use. Transendothelial chemotaxis was examined as described previously (35). Briefly, HUVEC were cultured for 1 wk on fibronectin-coated Transwell inserts (6.5 mm diameter, 5 μm pore size) (Costar Corp., Cambridge, MA). Inserts were transferred onto lower chambers containing 500 μl of the supernatants, eosinophils (2.5 × 106) suspended in 100 μl of 10% FCS plus RPMI 1640 were added to each insert, and the cells that transmigrated to the lower chambers after 1 h were counted by FACS® as described previously (17).

Static adhesion assay. Purified ICAM-1 or VCAM-1 was diluted to 25 μg/ml in PBS (pH 9.0) and immediately spotted onto wells (35 mm) of a six-well culture plate. After 2 h incubation at 37°C, the wells were washed twice with RPMI 1640 and blocked with 20 μg/ml HSA (Calbiochem Corp.) for 24 h at 4°C. After washing, 0.5 ml of the HUVEC culture supernatants were added and prewarmed in the 37°C incubator for 10 min. Eosinophils (106) suspended in 0.5 ml of 10% FCS plus RPMI 1640 were then added to the well and placed at 37°C for 3 min after which all the cells had settled to the bottom of the well. The wells were then gently washed with 2.0 ml of warmed assay medium five times, and the cells bound to the substrate were counted in three different fields under the microscope.

Laminar flow assay. A parallel-plate flow chamber (36) was mounted on a HUVEC monolayer cultured in a six-well plate (35 mm in diameter), placed on the stage of a phase–contrast microscope, and monitored with a ×20 objective (3, 37). Wall shear stress was calculated as described previously (3). Eosinophils suspended in 1.0 ml of assay medium were perfused on the HUVEC monolayer for 3 min through the flow chamber using an automated syringe pump (Harvard Apparatus, Inc., South Natick, MA) attached to the outlet side. In some experiments, the shear flow was increased to 10, 20, and 40 dyn/cm2 for 10 s each after 3 min perfusion at 1.5 dyn/cm2, and cells remaining at the end of each shear were calculated as the percentage of the total number of cells observed just before the increase in shear to 10 dyn/cm2. Cells interacting with the substrate during flow were analyzed with the images videotaped with a video camera (TEC-470 CCD; Optronics, Goleta, CA) and recorder (HI-8 CVD-1000; Sony Corp., Park Ridge, NJ).

Evaluation of tethering and accumulation, and enumeration of arrested, rolling, and detached cells. Tethered cells were defined as cells that maintained an adhesive interaction with the HUVEC monolayer for at least 1 s. The number of tethers was counted over the initial 1 min after the flow became stable. For the analysis of posttethering behavior, the movement of each tethered cell was observed carefully for another 30 s after it first tethered on the monolayer. Cells detached in the flow stream in this 30 s were counted as detached cells. Among the cells that remained adherent in this period, cells that were displaced less than or more than one cell diameter for the 30 s were defined as arrested and rolling cells, respectively. Total cell accumulation was defined as the number of the cells that arrested at 3 min after the flow became stable. P values were calculated by paired Student’s t test, and the differences with P < 0.05 were considered to be significant.

Results

HUVEC activated with TNF-α and IFN-γ produce chemokines for eosinophils. The culture supernatants of HUVEC were examined for chemotactic activities for purified eosinophils with a transendothelial migration assay (Fig. 1 A). Few eosinophils migrated to assay medium or supernatants of unstimulated or IL-4–stimulated HUVEC. However, significantly more eosinophils transmigrated to supernatants of HUVEC stimulated with 100 U/ml TNF-α or 100 U/ml IFN-γ. The combination of TNF-α and IFN-γ produced synergistic effects for eosinophil chemotaxis (Fig. 1 A). Pretreatment with the mAb to CCR3 reduced eosinophil chemotaxis to the supernatant from TNF-α and IFN-γ–stimulated HUVEC to the same level as that to control supernatant, whereas mAb to IL-8RA (CXC1R1) showed no effect (Fig. 1 B).

Eosinophil binding to immobilized ICAM-1 or VCAM-1 was examined with a 3-min static assay. Supernatants from HUVEC activated with TNF-α and IFN-γ increased markedly eosinophil adhesion to ICAM-1 (Fig. 2, left, no mAb). This enhancement of binding to ICAM-1 was blocked almost completely by CCR3 mAb but not by IL-8RA mAb (Fig. 2, left). By contrast to ICAM-1, unstimulated eosinophils showed marked binding to VCAM-1 (Fig. 2, right). However, supernatant from activated HUVEC increased the adhesion to VCAM-1 by approximately twofold (Fig. 2, right, no mAb). Again, this stimulated binding to VCAM-1 was inhibited almost completely by CCR3 mAb (Fig. 2, right).

CCR3 mAb partially reduces eosinophil arrest and accumulation on HUVEC activated with TNF-α and IFN-γ. Accumulation of eosinophils after 3 min perfusion at a wall shear stress of 1.5 dyn/cm2 on activated HUVEC was reduced by 22±4.7% by CCR3 mAb (Fig. 3, right). Although inhibition was not as prominent as in static experiments, it was reproducible in all of seven different experiments (6.5–32% inhibition), and the dif-
ference was statistically significant \((P < 0.005, n = 7)\). Cells that interacted with the endothelial monolayer, i.e., tethered, during the first 1-min period were individually monitored and enumerated according to their behavior during the 30-s period subsequent to tethering as arrested, rolling, or detaching cells (Fig. 3, left). Almost all control eosinophils arrested abruptly shortly after tethering, i.e., without intervening rolling, and few cells detached within the following 30 s. A significantly greater number of CCR3 mAb-treated cells detached \((P < 0.01, n = 7)\), and the number of arrested cells was decreased significantly, by \(20 \pm 5.4\% \) \((P < 0.02, n = 7)\). This clearly indicates that the stimulation of CCR3 by HUVEC-derived chemoattractants is at least in part responsible for eosinophil arrest formation in shear flow. However, almost all detachment was observed within 30 s after the initial tethering and rarely thereafter. Moreover, even in anti-CCR3–treated cells, the majority of the adherent cells still showed immediate arrest, with few rolling cells (Fig. 3, left).

**CCR3 mAb partially blocks both \(\alpha_4\) and \(\beta_2\) integrin activation.** Since eosinophils have been shown to functionally express \(\alpha_4\) as well as \(\beta_2\) integrins \((38–41)\), we next examined the effect of the anti-CCR3 mAb together with the mAbs to \(\alpha_4\) as well as \(\beta_2\) integrins. As already described for experiments on TNF-\(\alpha\)–stimulated HUVEC \((42)\), the \(\alpha_4\) integrin mAb HP2/1

![Figure 2](image1.png)

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partially reduced eosinophil arrest and induced rolling or detachment in approximately half of the tethered eosinophils (Fig. 4, left). This resulted in a 36±3.7% decrease in eosinophil accumulation on HUVEC activated with TNF-α and IFN-γ ($P < 0.05, n = 4$) (Fig. 4, right). However, CCR3 mAb gave additional inhibition, and the effect of CCR3 mAb on α4 integrin–blocked eosinophils was more prominent than on control eosinophils. Compared with treatment with α4 mAb alone, addition of CCR3 mAb further decreased eosinophil arrest by 41±11% ($P < 0.01, n = 4$), increased detachment two-fold ($P < 0.05, n = 4$) (Fig. 4, left), and decreased total cell accumulation by 49±11% ($P < 0.01, n = 4$) (Fig. 4, right). β2 integrin mAb TS1/18 had little effect on eosinophil accumulation, although treatment with α4 and β2 mAb together blocked almost completely eosinophil arrest and accumulation. In the presence of β2 integrin mAb, CCR3 mAb partially decreased arrest and increased detachment, and resulted in a 26±7.0% reduction in total accumulation ($P < 0.05, n = 4$).

![Figure 3](image-url). Effect of CCR3 mAb on eosinophil behavior after tethering and accumulation on activated HUVEC. HUVEC monolayers were stimulated with 100 U/ml of TNF-α and IFN-γ for 24 h, and eosinophils treated with each mAb were resuspended in HBSS with 10 mM Hepes including 2 mM Ca$^{2+}$, 1 mM Mg$^{2+}$, and 10% FCS, pH 7.4, and perfused on the monolayer for 3 min at 1.5 dyn/cm$^2$. Cells that tethered in the first minute were enumerated for subsequent arrest (gray bars), rolling (dotted bars), or detachment (white bars), and total accumulation was evaluated at 3 min. Data show mean±SD in seven independent experiments. *$P < 0.05$, **$P < 0.01$.

![Figure 4](image-url). Effect of CCR3 mAb on behavior after tethering and accumulation of α4 or β2 integrin–blocked eosinophils. Eosinophils were pre-treated with mAbs to integrins and chemokine receptors and perfused on HUVEC stimulated with TNF-α and IFN-γ using the same conditions as in the citation to Fig. 3. Measurements were as in Fig. 3. Data show mean±SD in four independent experiments. *$P < 0.05$, **$P < 0.01$. 

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all experimental conditions, IL-8RA mAb had no inhibitory effect (Fig. 4).

**Effect of platelet-activating factor (PAF) antagonist or PTx on eosinophil arrest and accumulation on activated HUVEC.**
In the same experimental system, we examined the effect of PAF antagonist or PTx. UK-74505, one of the most potent PAF antagonists (43, 44), at either $10^{-7}$ or $10^{-6}$ M concentration showed no significant effect on eosinophil tethering, arrest, and accumulation whether used alone or together with CCR3 mAb (Fig. 5 A). PTx has been shown previously to block CCR3-dependent eosinophil responses (18, 19). 2-h incubation with PTx but not with CTx significantly decreased eosinophil arrest and accumulation, by $17 \pm 1.2\%$ ($P < 0.05$, $n = 4$) and $23 \pm 3.4\%$ ($P < 0.05$, $n = 4$), respectively (Fig. 5 B). However, the amount of inhibition with PTx was the same as with CCR3 mAb.

**Discussion**
In this study, we examined how chemoattractants produced in situ affect eosinophil adhesive interactions with endothelial cells in shear flow using a function-blocking mAb to CCR3. Our data show that TNF-α and IFN-γ–stimulated HUVEC produced chemoattractants for eosinophils, consistent with a previous report demonstrating RANTES production by cytokine-stimulated HUVEC (45). Furthermore, supernatant from activated HUVEC enhanced eosinophil binding to immobilized ICAM-1 and VCAM-1 in a 3-min static assay, suggesting that chemokines can activate both α4 and β2 integrins within minutes. Importantly, stimulation of chemotaxis and adhesion by eosinophils was abrogated completely by pretreatment with the CCR3 mAb. These results confirm inhibition of responses to specific chemokines in a previous study (28), and further suggest that even if the activated HUVEC produce some other unknown chemoattractants, their effects on eosinophils are entirely through CCR3. This validated the use of CCR3 mAb for evaluation of the effect of chemoattractants released by activated HUVEC on eosinophil interactions in shear flow.

As reported for TNF-α–activated HUVEC (42), most tethered eosinophils did not roll, but arrested abruptly on TNF-α and IFN-γ–activated HUVEC monolayers under physiological shear stress. Treatment with CCR3 mAb partially but signifi-
cantly decreased eosinophil accumulation. Videotape analysis revealed that the treatment did not affect the total number of tethered eosinophils, but inhibited conversion of tethered cells to firmly adherent cells and thus increased the percentage of cells that detached from the monolayer within the next 30 s after tethering. This indicates that the HUVEC-derived chemokines enhance eosinophil adhesiveness within seconds and thus prevent the detachment of eosinophils tethered on the HUVEC surface. Detachment of the tethered cells was observed mostly within the 30 s immediately after tethering, and cells that remained adherent beyond 30 s rarely rolled or detached thereafter. This is not surprising, because chemotactant stimulation often shows peak responses in Ca$$^{2+}$$ influx or actin polymerization within 30 s (11, 46–48). However, the majority of the anti-CCR3–treated eosinophils still showed immediate arrest, with only a few rolling cells. PTx–treated eosinophils were similarly capable of almost immediate arrest after tethering, with little intervening rolling.

This behavior may be attributed to the functional expression of $$a_4$$ integrins in eosinophils. Consistent with our previous findings (42), eosinophil arrest on activated HUVEC was dependent mostly on $$a_4$$ integrin and only partially on $$b_2$$ integrin. In the presence of $$a_4$$ mAb, approximately half of eosinophil arrest and accumulation was abrogated by CCR3 mAb. By contrast, CCR3 mAb had less effect on $$b_2$$ integrin–blocked eosinophils, and inhibited to almost the same level as when no antiintegrin mAb was used. Moreover, comparing groups that were all treated with CCR3 mAb, the addition of $$a_4$$ mAb reduced accumulation by half ($P < 0.05$, $n = 4$), but $$b_2$$ mAb had very little effect ($P > 0.1$, $n = 4$). These findings imply that $$a_4$$ integrins on eosinophils have considerable potential to mediate eosinophil arrest on activated HUVEC, even without exposure to chemotactants. This may make the effect of CCR3 mAb less prominent in flow experiments. Indeed, $$a_4$$ integrin has been shown to support leukocyte adhesion even in the presence of shear stress (49, 50), and to be mainly responsible for monocyte or lymphocyte arrest on endothelial cells under physiological shear conditions (51, 52). In contrast, $$b_2$$ integrins are unable to support leukocyte adhesion in physiological shear flow without the participation of other adhesion molecules to mediate tethering and rolling (3). The functional difference between $$a_4$$ and $$b_2$$ integrins may also explain the higher binding of unstimulated eosinophils to VCAM-1 than to ICAM-1 in static assays.

The lack of complete inhibition of adhesion in flow to stimulated HUVEC by CCR3 mAb, even in the presence of $$a_4$$ mAb, contrasted with results in chemotaxis and static adhesion assays. This indicates that the role of chemotactants in eosinophil arrest on endothelium may be less important than in the following transmigration step, and that other mechanisms may be important in arrest. An alternative mechanism for activation of integrins is through stimulation by PAF, because PAF has been shown to be produced by TNF-$$\alpha$$–stimulated HUVEC (53) and to use a receptor distinct from CCR3 (54). In static experiments, PAF has been found to stimulate neutrophil $$b_2$$ integrins in cooperation with P-selectin (55, 56). Furthermore, PAF produced from TNF-$$\alpha$$–stimulated HUVEC is mostly surface associated and is not released as the soluble factor (53). A PAF antagonist partially reduced neutrophil attachment to TNF-$$\alpha$$– or thrombin-stimulated HUVEC in flow (57). Therefore, we perfused eosinophils pretreated with a PAF receptor antagonist, UK-74505, on the activated HUVEC under the same shear conditions. However, the antagonist, at either known optimal or higher concentrations, showed no significant effect on eosinophil arrest or accumulation. The reason for this discrepancy between eosinophils and neutrophils is not clear, but might be caused by the differential effects of PAF on activating $$a_4$$ or $$b_2$$ integrins, since there are some reports suggesting that PAF can increase eosinophil binding to ICAM-1 (58) and mucosal addressin cell adhesion molecule 1 (59) but not to VCAM-1 (59). To test whether activation might occur through yet other G protein–coupled receptors on eosinophils, we examined the effect of PTx treatment. PTx treatment partially decreased eosinophil arrest and accumulation; however, the inhibitory effect did not exceed that of anti-CCR3 mAb. From these results, it appears that PAF or other chemotactants that might be retained on the HUVEC surface and do not bind CCR3 have little role in eosinophil arrest on endothelium.

It has been proposed that selectin-mediated interactions can trigger integrin activation. Several studies have shown that binding to E-selectin (60–62) or cross-linking of L-selectin (63, 64) enhances $$b_2$$ integrin–mediated adhesion, although there is no evidence that P-selectin directly activates the $$b_2$$ integrin. In eosinophils, tethering is dependent mainly on P-selectin and partially on L-selectin but not on E-selectin (42, 65, 66). We have observed that blockade of P- or L-selectin by mAbs partially decreased the tethering efficiency of eosinophils but did not affect posttethering behavior (42). This suggests that selectin-mediated adhesion is not responsible for integrin activation and eosinophil arrest on activated HUVEC.

In summary, chemokines produced by TNF-$$\alpha$$ and IFN-$$\gamma$$–stimulated endothelium can act through CCR3 to enhance the avidity of both $$a_4$$ and $$b_2$$ integrins of eosinophils. Adhesion strengthening occurs within seconds and augments eosinophil accumulation in shear flow by converting transiently tethered cells to arrested cells. Although the role of chemokines in arrest and accumulation of eosinophils on stimulated endothelium appears to be less prominent than in transmigration, our study is the first to demonstrate that locally produced chemokines are actually involved in leukocyte arrest and accumulation on endothelium in shear flow.

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References

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