Resveratrol Suppresses Tumor Necrosis Factor-α-Induced Fractalkine Expression in Endothelial Cells

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Received January 11, 2006; accepted April 13, 2006

ABSTRACT

Up-regulation of fractalkine is involved in vascular and tissue damage in inflammatory conditions. Resveratrol has been shown to have anti-inflammatory, antioxidant, and antitumor activities. Its regulatory effects on expression of fractalkine in vascular endothelial cells and fractalkine receptor CX3CR1 in monocytes have not been studied. We evaluated the effects of resveratrol on fractalkine expression in human umbilical vein endothelial cells and CX3CR1 expression in THP-1 cells in response to treatment with tumor necrosis factor (TNF)-α. TNF-α significantly induced fractalkine mRNA and protein expression in endothelial cells. Resveratrol strongly suppressed TNF-α-induced fractalkine expression in endothelial cells through suppression of nuclear factor-κB and Sp1 activities. Resveratrol decreased the number of TNF-α-induced fractalkine-positive endothelial cells and CX3CR1-positive cells determined by flow cytometric analysis. Resveratrol suppressed TNF-α-stimulated monocytes adhesion to human umbilical vein endothelial cells. Immunohistochemical analysis revealed that resveratrol suppressed TNF-α-induced arterial endothelial fractalkine expression in heart, kidney, and intestine and decreased ED-1-positive cell infiltration in intestinal villi. Resveratrol may provide a new pharmacological approach for suppressing fractalkine/CX3CR1-mediated injury in inflammatory conditions.

Adherence of circulating inflammatory cells and migration to the subendothelial space is an initial process in inflammatory conditions (Gimbrone et al., 1997; Cines et al., 1998). Chemokines in endothelial cells and those receptors in inflammatory cells are critical in the initiation, maintenance, and resolution of inflammation (Fujiwara and Kobayashi, 2005). Fractalkine (CX3CL1) is the only CX3C-chemokine in which a soluble chemokine-like domain is fused to a mucin stalk that extends across the cell membrane into the cytoplasm (Bazan et al., 1997; Pan et al., 1997). The expression of membrane-bound fractalkine can be markedly induced on primary endothelial cells by inflammatory cytokines, such as interferon-γ, interleukin-1 and tumor necrosis factor (TNF)-α (Garcia et al., 2000). Fractalkine can function as both a chemoattractant and an adhesion molecule for its receptor, CX3CR1 (Imai et al., 1997; Haskell et al., 1999).

Expression of CX3CR1 and migration toward fractalkine have been demonstrated for monocytes/macrophages, some T cells, and natural killer cells (Imai et al., 1997; Fong et al., 1998; Harrison et al., 1998; Foussat et al., 2000). Thus, fractalkine expressed on inflamed endothelium may be a vascular gateway for CX3CR1-expressing cells by rapidly capturing them from the blood and promoting their migration into tissue. Because up-regulation of fractalkine is involved in vascular and tissue damage in various diseases, such as atherosclerosis (Lesnik et al., 2003), glomerulonephritis (Segerer et al., 2002), cardiac allograft rejection (Robinson et al., 2000), HIV infection (Foussat et al., 2001), and rheumatoid arthritis (Nanki et al., 2004), down-regulation of fractalkine expression can be important in preventing and treating these diseases. Only a few substances—the soluble form of interleukin-6 receptor-α (Matsumiya et al., 2001) and 15-deoxy-Δ12,14-prostaglandin J2 (Imaizumi et al., 2002)—and hypoxia (Yamashita et al., 2003) were reported to inhibit

ABBREVIATIONS: TNF, tumor necrosis factor; HIV, human immunodeficiency virus; NF, nuclear factor; HUVEC, human umbilical vein endothelial cell; PD98059, 2’-amino-3’-methoxyflavone; MG-132, N-benzyloxy carbonyl [Z]-Leu-Leu-leucinal; H-89, N-[2-(4-bromocinnamylamino)ethyl]-5-isoquinoline; RPA, RNase protection assay; EMSA, electrophoretic mobility shift assay.
fractalkine expression in endothelial cells. We have reported that \( \alpha \)-lipoic acid reduces fractalkine-mediated inflammatory processes in endotoxemia (Ahn et al., 2004; Sung et al., 2005). It is well known that CX3CR1 is expressed in monocytes/macrophages and is the mechanism of monocytes/macrophages capture, firm adhesion, and activation (Fong et al., 1998). A polymorphism in the CX3CR1 gene was also reported to be associated with low CX3CR1 expression and reduced risk of acute coronary disease in humans (Combadiere et al., 2003). Because fractalkine and CX3CR1 are critical to inflammation, therapeutic interventions that target fractalkine in endothelial cells and CX3CR1 in monocytes/macrophages may open new avenues for controlling inflammatory diseases.

Resveratrol (\( \text{trans-3',4',5'-trihydroxy-trans-stilbene} \)), a polyphenolic compound present in grapes and red wine, has been reported to have a cardioprotective effect via an antioxidative effect (Frankel et al., 1993; Fauconneau et al., 1997), cancer chemopreventive activity (Jang et al., 1997), suppression of cellular smooth muscle proliferation/migration (Araim et al., 2002), and inhibition of platelet aggregation (Pace-Acsiak et al., 1996). At concentrations present in human plasma after moderate wine consumption, resveratrol inhibits the expression of adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin by agonist-stimulated endothelial cells (Bertelli et al., 2001; Pendurthi and Rao, 2002). Ferrero et al. (1998) have also reported that resveratrol reduces granulocyte and monocyte adhesion to endothelial cells. The anti-inflammatory activity of resveratrol may be related to interference with the nuclear factor (NF)-\( \kappa \)B signaling pathway, which regulates the expression of various genes involved in inflammation (Tsai et al., 1999; Manna et al., 2000). However, the effects of resveratrol on fractalkine expression and its signal pathway in endothelial cells and on CX3CR1 expression in monocytes/macrophages have not been examined.

In this study, we examined whether resveratrol decreases the expressions of TNF-\( \alpha \)-induced fractalkine in human umbilical vein endothelial cells (HUVECs) and TNF-\( \alpha \)-induced CX3CR1 in THP-1 cells. Furthermore, we evaluated the role of resveratrol in TNF-\( \alpha \)-induced endothelial fractalkine expression in vivo. Our results show that resveratrol prevents the expressions of TNF-\( \alpha \)-induced CX3CR1 in THP-1 cells and rat ED-1-positive monocytes/macrophages were used according to a method described previously (Sung et al., 2005).

Materials and Methods

**Materials and Cell Culture.** Anti-fractalkine antibody (full-length) and anti-CX3CR1 antibody were purchased from Torrey Pines BioLabs (Houston, TX). Anti-phospho-p65 (Ser536) and anti-p65 antibodies were from Cell Signaling Technology (Beverly, MA). Anti-p65, anti-p50, and anti-Sp1 for gel shift assay were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Mitogen-activated protein kinase kinase 1/2 inhibitor DP98059, NF-\( \kappa \)B inhibitor MG-132, protein kinase C inhibitor calphostin C and H-89 were purchased from Calbiochem (San Diego, CA). Resveratrol, the phosphatididylinositol 3'-kinase inhibitor wortmannin, the NF-\( \kappa \)B inhibitor pyrrolidine dithiocarbamate, TNF-\( \alpha \), media, sera, and most other biochemical reagents were from Sigma-Aldrich (St. Louis, MO) unless otherwise specified. HUVECs were prepared from human umbilical cords by collagenase digestion as described previously (Ahn et al., 2004). THP-1 cells were from American Type Culture Collection (Manassas, VA).

**R\( \text{N} \)ase Protection Assay and Immunoblotting.** RPA and immunoblotting were performed as described previously (Ahn et al., 2004). The membrane was reblotted with anti-actin antibody to verify equal loading of protein in each lane.

**Monocyte Isolation and Adhesion Assay.** The study protocol and informed consent forms were approved by the Chonbuk National University Hospital Review Board, and subjects were given informed consent. Human peripheral blood monocytes were isolated from fresh blood from healthy volunteers by Ficoll-Paque gradient centrifugation. Monocytes were further purified by negative selection using magnetic beads (Miltenyi Biotec, Bergisch Gladbach, Germany) (Ancuta et al., 2003). Monocyte-endothelial adhesion was determined by previously used methods (Kim et al., 2003).

**Flow Cytometry.** For flow cytometry analysis for fractalkine, HUVECs were treated as described previously (Sung et al., 2005). For flow cytometry analysis for CX3CR1, THP-1 cells and rat ED-1-positive monocytes/macrophages were used according to a method described previously (Sung et al., 2005).

**Electrophoretic Mobility Shift Assay.** EMSA for NF-\( \kappa \)B and Sp1 proteins were performed as described previously (Ahn et al., 2004). Signals were detected by chemiluminescent imaging according to the manufacturer’s protocol (EMSA Gel-Shift kit; Panomics, Redwood City, CA).

**Luciferase Assay.** HUVECs were plated at a density of 5.0 \( \times 10^5 \) cells per well on 24-well plates and transfected using SuperFect transfection reagent (QIAGEN, Hilden, Germany) in serum-free medium for 14 days (Arichi et al., 1982). Control (vehicle) rats similarly received 0.3% carboxymethyl cellulose solution and given to rats by oral intubation at a dose of 50 mg in 0.5 ml of 0.3% solution/kg daily for 14 days (Arichi et al., 1982). Control (vehicle) rats similarly received 0.3% carboxymethyl cellulose solution alone. Control buffer and TNF-\( \alpha \) were then injected intravenously through the tail vein. Twelve hours after injection of vehicle or TNF-\( \alpha \), rats were anesthetized with ketamine (100 mg/kg) and xylazine (10 mg/kg) and sacrificed by cervical dislocation. Heart, kidney, and intestine were harvested for immunohistochemical analysis.

**Immunohistochemical Analysis of Fractalkine and ED-1.** Immunohistochemical analysis was performed as described previously (Sung et al., 2005).
Densitometric Analyses and Statistics. Data are expressed as mean ± S.D. Statistical significance was tested using Student’s t test or one-way analysis of variance followed by the Student-Newman-Keuls test. Statistical significance was set at p < 0.05.

Results

TNF-α Increased Expression of Fractalkine mRNA and Protein in HUVECs. We reported previously that TNF-α produces a maximal effect on the expression of fractalkine mRNA in HUVECs at 4 h (Ahn et al., 2004). Therefore, we examined the effect of various concentrations of resveratrol on TNF-α-induced fractalkine mRNA at this time. TNF-α (10 ng/ml) also increased the expression of fractalkine mRNA in a dose-dependent manner.

Addition of TNF-α (10 ng/ml) maximally increased expression of fractalkine protein at 6 h, and the level continued to be higher than control for up to 24 h. The maximum mean increase in fractalkine was 9.5-fold.

Inhibitors Changed TNF-α-Stimulated Expression of Fractalkine mRNA. We reported previously that NF-κB inhibitor MG-132 and pyrrolidine dithiocarbamate suppressed TNF-α-induced expression of fractalkine mRNA (Ahn et al., 2004). However, the phosphatidylinositol 3'-kinase inhibitor wortmannin, the mitogen-activated protein kinase kinase 1/2 inhibitor PD98059, the protein kinase C inhibitor calphostin C, and the protein kinase A inhibitor H-89 produced no changes. These results suggest that TNF-α-stimulated expression of fractalkine might be mediated mainly through activation of NF-κB pathways.

Resveratrol Suppressed TNF-α-Induced Fractalkine mRNA and Protein in HUVECs. Because TNF-α produces a maximal effect on the expression of fractalkine mRNA in HUVECs at 4 h, we examined the effect of various concentrations of resveratrol on TNF-α-induced fractalkine mRNA at this time. Resveratrol suppressed TNF-α-induced expression of fractalkine mRNA in a dose-dependent manner (Fig. 1A). Resveratrol at 0.5 μM suppressed approximately 20 to 30% of TNF-α-induced expression of fractalkine mRNA; higher concentrations of resveratrol (5 and 10 μM) almost completely suppressed TNF-α-induced fractalkine mRNA expression. However, a high concentration of resveratrol (5 μM) alone did not significantly affect on the mRNA levels of fractalkine. In agreement with the RPA data, resveratrol at 1 μM suppressed approximately 30 to 40% of TNF-α-induced expression of fractalkine protein, whereas resveratrol at 5 and 10 μM almost completely suppressed TNF-α-induced fractalkine protein expression (Fig. 1B).

Resveratrol Reduced the Number of Fractalkine-Positive Cells in TNF-α-Stimulated HUVECs. The number of fractalkine-positive cells was increased approximately 6-fold in HUVECs after stimulation with TNF-α; after resveratrol treatment, the number was decreased to the control level by flow cytometry (Fig. 1C). These data suggest that resveratrol inhibited TNF-α-induced fractalkine expression in HUVECs.

Resveratrol Reduced CX3CR1 Protein and the Number of CX3CR1-Positive Cells in TNF-α-Stimulated THP-1 and ED-1-Positive Monocytes/Macrophages. In Western blot analyses, TNF-α increased CX3CR1 protein level approximately 3.0-fold at 6 h in THP-1 cells (Fig. 2A). Resveratrol suppressed TNF-α-induced expression of CX3CR1 protein in a dose-dependent manner (Fig. 2A). Addition of resveratrol at 1 μM suppressed approximately 17% of TNF-α-induced expression of CX3CR1 protein, whereas...
Resveratrol decreased the number of CX3CR1-positive cells in TNF-α-stimulated THP-1 cells. A, Western blot analyses of CX3CR1 protein in TNF-α-stimulated THP-1 cells cotreated with resveratrol (Res). THP-1 cells were incubated for 6 h with CB, TNF-α (10 ng/ml), or TNF-α plus the indicated amount of Res. Western blot was probed with an anti-CX3CR1 antibody and reprobed with an anti-actin antibody to verify equal loading of protein in each lane. Densitometric analyses are presented as the relative ratio of each protein to actin. The ratio relative to CB is arbitrarily presented as 1. Results were similar in three independent experiments. Bars represent the mean ± S.D.

B, analyses of CX3CR1 expression in HUVECs detected by flow cytometry. THP-1 cells incubated with control buffer (CB), Res (5 μM), TNF-α (10 ng/ml), or TNF-α (10 ng/ml) plus Res (5 μM) for 6 h.

Resveratrol suppressed TNF-α-induced endothelial adhesiveness for monocytes. A, fluorescent microscopic findings of endothelial adhesiveness for monocytes. Scale bar, 50 μm. B, quantification of monocytes adhesion to HUVECs. Monocytes, fluorescently labeled with calcein-AM (50 μM), were added to confluent monolayers of HUVECs, which were treated with TNF-α (10 ng/ml) for 6 h and were also treated with control buffer (CB), resveratrol (Res, 5 μM), or anti-fractalkine antibody (20 μg/ml). More monocytes were found in HUVECs treated with TNF-α than with CB. Note that treatment with TNF-α plus Res or anti-fractalkine antibody decreased the TNF-α-induced increase of monocyte adhesion to HUVECs. Bars represent the mean ± S.D. from four experiments. *, p < 0.05 versus CB; #, p < 0.05 versus TNF-α.
higher concentrations of resveratrol (5 μM) suppressed to the control level. However, a high concentration of resveratrol (5 μM) alone did not significantly affect the protein levels of CX3CR1 (Fig. 2A).

The number of CX3CR1-positive cells was increased approximately 2.5-fold in THP-1 cells after stimulation with TNF-α; after resveratrol treatment, the number was decreased to the control level by flow cytometry (Fig. 2B). We also used flow cytometry to evaluate the change in the number of CX3CR1-positive cells in ED-1-positive monocytes/macrophages prepared from rats treated with TNF-α. Compared with the control cells, the number of CX3CR1-positive cells in ED-1-positive monocytes/macrophages was increased approximately 2.7-fold at 12 h. Pretreatment with resveratrol (50 mg/kg per day) decreased the number of TNF-α-induced CX3CR1-positive cells in ED-1-positive monocytes/macrophages by approximately 47%. These results indicate that resveratrol inhibits the TNF-α-induced CX3CR1 expression in THP-1 cells and in ED-1-positive monocytes/macrophages in rat blood.

**Resveratrol Suppressed TNF-α-Induced Monocyte Adhesiveness to HUVECs.** Because the induction of fractalkine in endothelial cells induces monocyte adhesion (Ancuta et al., 2003), we examined whether resveratrol decreases monocyte adhesion to TNF-α-stimulated HUVECs. Stimulation of HUVECs with TNF-α (10 ng/ml) for 6 h induced a significant increase (~4.7-fold) in monocyte adhesion compared with treatment with control buffer but treatment with resveratrol led to a 58% decrease in monocyte adhesion (Fig. 3). Furthermore, treatment of TNF-α-stimulated cells with an anti-fractalkine antibody led to a 50% decrease in monocyte adhesion; resveratrol or the anti-fractalkine antibody alone had no effect. These findings suggest that resveratrol decreases monocyte adhesion to TNF-α-stimulated HUVECs through fractalkine expression.

**Resveratrol Suppressed TNF-α-Induced NF-κB and Sp1 Activities.** We demonstrated previously that TNF-α stimulated the expression of fractalkine mRNAs mainly through activation of NF-κB (Ahn et al., 2004). Therefore, we examined the effect of resveratrol on NF-κB activities using a phosphospecific anti-p65 antibody that detects only the p65 subunit of NF-κB when it is phosphorylated at Ser536. TNF-α induced the phosphorylation of the p65 subunit (~3.1-fold) at 15 min; this phosphorylation was nearly completely inhibited by cotreatment with resveratrol (5 μM) for 4 h (Fig. 4, A and B); resveratrol alone had no effect. To identify NF-κB and Sp1-binding complexes induced by TNF-α, nuclear extracts of HUVECs were subjected to a supershift assay. As shown in Fig. 4, C and F, incubation with p65, p50, or Sp1 antibodies produced slowly migrating complexes, indicating that NF-κB p65/p50, p50/p50, and Sp1 complexes were activated by TNF-α treatment. We also used EMSA to examine whether resveratrol inhibits NF-κB and Sp1 activities in nuclear extracts of HUVECs stimulated with TNF-α.
NF-κB (p65/p50) and Sp1 binding was increased in nuclear extracts from TNF-α-stimulated HUVECs, whereas cotreatment with TNF-α and resveratrol suppressed NF-κB and Sp1 binding (Fig. 4, D and G). To examine NF-κB- and Sp1-dependent transcriptional activities, we transiently transfected HUVECs with NF-κB- or Sp1-responsive luciferase reporter constructs. The day after transfection, cells were treated with TNF-α, resveratrol, or TNF-α plus resveratrol for 6 h, and then luciferase activity was determined. Treatment with resveratrol reduced NF-κB and Sp1 transcriptional activities induced by TNF-α (Fig. 4, E and H). These data suggest that resveratrol suppressed fractalkine expression through suppression of NF-κB and Sp1 activities in HUVECs.

Resveratrol Suppressed TNF-α-Induced Fractalkine Expression in Cardiac, Kidney, and Small Intestinal Endothelial Cells. Similar to our previous report (Ahn et al., 2004), intravenous injection of TNF-α (10 μg/kg) markedly increased fractalkine expression at 12 h in arterial endothelial cells in the heart. In the kidney, TNF-α increased fractalkine expression in arterial endothelial cells but not in glomerular endothelial and tubular epithelial cells. In the small intestine, TNF-α increased fractalkine expression in arteriolar endothelial cells and villous endothelium but not in lymphatic endothelial cells and epithelial cells. Pretreatment with resveratrol (50 mg/kg per day) dramatically suppressed TNF-α-induced fractalkine expression in arterial endothelial cells in heart, kidney, and small intestine (Fig. 5). Resveratrol also decreased TNF-α-induced villous endothelial fractalkine expression (Fig. 5). These findings suggest that resveratrol suppresses TNF-α-induced fractalkine expression in cardiac, kidney, and small intestinal endothelial cells.

Resveratrol Suppressed TNF-α-Induced ED-1-Positive Cell Infiltration in Intestinal Villi. Immunohistochemical examination of rat intestinal villi revealed a 5.2-fold increase in ED-1-positive cell infiltration after TNF-α treatment (Fig. 6). Resveratrol treatment prevented TNF-α-induced accumulation of ED-1-positive cells in intestinal villi by approximately 60%, whereas resveratrol alone had no effect. There were significantly fewer infiltrated ED-1-positive cells in jejunal sections from rats treated with TNF-α and anti-fractalkine antibody than in those treated with TNF-α and control antibody (Fig. 6). Anti-fractalkine antibody alone had no effect on ED-1-positive cell infiltration in jejunum. These results suggest that resveratrol decreased...
ED-1-positive macrophage infiltration into jejunum after TNF-α injection through regulation of fractalkine expression.

Discussion

In this study, we demonstrate that resveratrol suppressed endothelial fractalkine expression through the NF-κB-dependent signaling pathway and also decreased TNF-α-induced expression of CX3CR1 in monocytes. We also demonstrate that resveratrol decreases arterial endothelial fractalkine expression in heart, kidney, jejunum, and intestinal villous endothelial cells after TNF-α stimulation. Resveratrol also decreased TNF-α-induced ED-1-positive cell infiltration in intestinal villi. To our knowledge, this is a novel mechanism of the anti-inflammatory effect of resveratrol through the down-regulation of fractalkine.

Fractalkine can mediate adhesion of leukocytes expressing CX3CR1, which include monocytes, natural killer cells, and some T lymphocytes (Imai et al., 1997; Fong et al., 1998; Harrison et al., 1998; Foussat et al., 2000). Atherosclerosis is a chronic inflammatory disease (Ross, 1999). Recruitment of circulating monocytes to the arterial intima can contribute to the formation of atherosclerotic lesions (Ross, 1999). A high expression of fractalkine in smooth muscle cells located in macrophage-rich areas of atherosclerotic plaques was observed in apoE−/− mice on a high-fat diet (Moatti et al., 2001). Moreover, CX3CR1−/− mice have less atheroma formation (Moatti et al., 2001). Thus, fractalkine/CX3CR1 play an important role in inflammation and formation of atherosclerosis. Our immunohistochemical analyses in heart, small intestine, and kidney revealed that administration of resveratrol suppressed TNF-α-induced fractalkine expression in cardiac, kidney, and small intestinal endothelial cells. Our data also demonstrated that resveratrol suppressed the CX3CR1 expression in monocytes after stimulation with TNF-α. Because fractalkine and CX3CR1 have an important role in inflammatory conditions, the down-regulation of fractalkine is important in preventing and treating these inflammatory diseases, including atherosclerosis.

Our results demonstrate that resveratrol significantly decreased TNF-α-induced mRNA and protein expression of fractalkine in HUVECs (Fig. 1). Our results indicate that 5 μM resveratrol is sufficient to suppress most of the TNF-α-mediated fractalkine expression. Previous studies showed that as little as 19 μM resveratrol can block the progression of carcinogenesis and induce terminal differentiation by 50% (Jang et al., 1997). Likewise, topical application of resveratrol at 25 μM can inhibit 98% of skin tumors in mice induced by 7,12-dimethylbenz(a)anthracene plus 12-O-tetradecanoylphorbol-13-acetate (Jang et al., 1997). Considering that each gram of fresh grape skin contains 50 to 100 μg (200–400 μM) resveratrol and red wine has 1.5 to 3 mg/l (Goldberg et al., 1995; Jang et al., 1997), the resveratrol concentration used in our study is achievable in vivo by consumption of grapes or wine.

A possible anti-inflammatory role of resveratrol could be related to an interference with the NF-κB signaling pathway, which regulates the expression of various genes involved in inflammation (Manna et al., 2000). However, it has been reported that short-term resveratrol treatment (30 min) does not inhibit NF-κB in HUVECs, but overnight treatment does (Pellegratta et al., 2003). Our results were similar to these data in short-term treatment (30–60 min) with resveratrol, but longer treatment with resveratrol (5 μM for 4 h) blocked the phosphorylation of the p65 subunit of NF-κB (Fig. 4).

We demonstrate that resveratrol has a novel mechanism of the anti-inflammatory effect through the down-regulation of fractalkine and CX3CR1. Thus, our data add new evidence of resveratrol as an inflammation-modulating agent or adjunctive therapy in inflammatory diseases, including atherosclerosis.

Acknowledgments

We thank Judith Dickson for help in preparing the manuscript and Jung Eun Lee for help with immunohistochemistry.

References


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