Adiponectin Inhibits the Production of CXC Receptor 3 Chemokine Ligands in Macrophages and Reduces T-Lymphocyte Recruitment in Atherogenesis

Yoshihisa Okamoto, Eduardo J. Folco, Manabu Minami, A.K. Wara, Mark W. Feinberg, Galina K. Sukhova, Richard A. Colvin, Shinji Kihara, Tohru Funahashi, Andrew D. Luster, Peter Libby

Abstract—Obese individuals often have low plasma adiponectin and concomitant chronic inflammation with a predisposition to metabolic and cardiovascular diseases. The present study reports a novel antiinflammatory action of adiponectin in human monocyte-derived macrophages (MΦ) suppressing T-lymphocyte accumulation in atherogenesis. RNA profiling of lipopolysaccharide-stimulated human MΦ identified CXC chemokine ligands (CXCLs), such as IP-10 (interferon [IFN]-inducible protein 10) (CXCL10), I-TAC (IFN-inducible T-cell α chemoattractant) (CXCL11), and Mig (monokine induced by IFN-γ) (CXCL9), T-lymphocyte chemoattractants associated with atherogenesis, among the top 14 transcripts suppressed by adiponectin. Real-time quantitative RT-PCR and ELISA verified that adiponectin inhibited expression of these chemokines at both the mRNA and protein levels in a concentration-dependent manner. Adiponectin reduced the release by lipopolysaccharide-stimulated MΦ of chemoattractant activity for CXC chemokine receptor 3–transfected (receptor for IP-10, Mig, and I-TAC) lymphocytes. Adiponectin decreased lipopolysaccharide-inducible IP-10 promoter activity in promoter-transfected THP-1 MΦ but did not change IP-10 mRNA stability. In lipopolysaccharide-stimulated MΦ, reduction of IFN-β by adiponectin preceded inhibition of IP-10 mRNA expression. Immunoblot and chromatin immunoprecipitation analyses demonstrated that adiponectin attenuated activation of the transcription factor IFN regulatory factor 3, involved in the MyD88-independent pathway of Toll-like receptor 4 signaling, and subsequent IFN regulatory factor 3 binding to IFN-α promoter. In vivo studies further demonstrated thatapolipoprotein E/ adiponectin double-deficient (apoE/H11001) mice had increased plasma IP-10 levels, accelerated T-lymphocyte accumulation in atheromata, and augmented atherogenesis compared with apoE single-deficient (apoE/H9251) mice. This study establishes that low levels of adiponectin associated with obesity, the metabolic syndrome, and diabetes favor T-lymphocyte recruitment and contribute to adaptive immune response during atherogenesis. (Circ Res. 2008;102:218-225.)

Key Words: adiponectin ■ atherogenesis ■ chemokine ■ macrophage ■ T lymphocyte

Obesity has become a major medical threat worldwide. Excessive adiposity causes a systemic chronic inflammatory state. For example, obesity elevates plasma levels of C-reactive protein, a biomarker of inflammation in vivo.1,2 Many prospective clinical studies indicate involvement of chronic low-grade inflammation in the pathogenesis of atherosclerosis.3–5 In addition, recent studies have shown that macrophage-induced inflammation in adipose tissue contributes to the pathogenesis of obesity-related insulin resistance.6,7 Adipose tissue produces a variety of bioactive molecules known as adipocytokines; the most abundant among them, adiponectin, accounts for 0.01% of total plasma protein.8–10 Interestingly, obese subjects have relatively low plasma levels of adiponectin.11 Adiponectin has emerged as a key protective adipocytokine in obesity-related metabolic and cardiovascular disorders, implicated in attenuation of insulin resistance, atherosclerosis, and cardiac remodeling.12–16 Hence the antiinflammatory effect of adiponectin appears biologically important. Several clinical studies have shown an inverse correlation between plasma levels of adiponectin and C-reactive protein.17–19 In addition, in experimental studies, adiponectin reduced the expression of the proinflammatory cytokine tumor necrosis factor (TNF)-α in arterial and adipose tissue.13,14 Importantly, in human monocyte-derived macrophages (MΦ), cells that localize in adipose tissue, adiponectin inhibits expression of interleukin-6 as well as TNF-α but augments levels of the antiinflammatory cytokine interleukin-10.20–22 Several previous studies suggest that adiponectin atten-
ulates inflammatory signaling pathways such as nuclear factor (NF)-κB21,23,24 However, knowledge of the antiinflammatory mechanisms of adiponectin in MΦ remains incomplete.

The present study identified novel antiinflammatory actions of adiponectin: strong inhibition of T-lymphocyte–active CXC chemokine receptor 3 (CXCR3) chemokine ligands in human lipopolysaccharide (LPS)-stimulated MΦ. In vivo data affirm that adiponectin regulates atherogenesis through this T-lymphocyte chemoattractant pathway. Our results clarify a role for adiponectin as a suppressor of T-lymphocyte recruitment, an important regulatory component in the development and complication of atherosclerotic plaques.

Materials and Methods

Cell Culture

Human monocyes/MΦ, human CXCR3-transfected, and parental untransfected 300-19 cell lines (gifts from B. Moser, Theodor-Kocher Institute, Bern, Switzerland) and THP-1 cells (American Type Culture Collection, Manassas, Va) were prepared as reported previously.25-27

Human MΦ Treatment

Differentiated MΦ were incubated in medium 199 containing 1% human serum with or without the indicated amount of insect cell–derived recombinant adiponectin (Nosan Corp) for 24 hours. Then, MΦ were stimulated with 5 ng/mL LPS (Calbiochem) or with 1000 U/mL interferon (IFN)-γ (Endogen) or 1000 U/mL IFN-ß (R&D Systems) for the indicated time. In mRNA stability experiments, 3 hours after LPS stimulation, the cells were treated with 5 μg/mL actinomycin D (Sigma) for the indicated time.

cDNA Microarray Screening

MΦ total RNA (10 μg each) from 4 independent donors treated in each experimental condition was tested for the cDNA microarray screening with Human Genome U133 Plus 2.0 chips using the Affymetrix GeneChip Laboratory Information Management System (Affymetrix, Santa Clara, Calif). The data are expressed as the fold or percentage changes of indicated gene expression between 2 different conditions.

Quantification of Gene Expression by Real-Time PCR

DNase I–treated total RNA from human MΦ or mouse aortic tissue was reverse transcribed, and real-time quantitative PCR with cDNA was performed on an iCycler IQ Real-Time PCR Detection System using SYBR Green I (Bio-Rad). The sequence of sense primers, antisense primers were as follows: human IP-10, 5'-GAGGC-TACAGCAGAGGAACC-3' and 5'-GAGTCAGAAAGATAAGG-3'; human I-TAC, 5'-GCTAAGCAGTTGGTGGTGCA-3' and 5'-CATCTCATAGATGGTCAATGC-3'; human I-FN-α, 5'-TCACCACCATGGAGAAGGC-3' and 5'-CATCGCCCCACTTGATT-3'; mouse CD4, 5'-GCTAAGCAGTTGGTGGTGCA-3' and 5'-CATCTCATAGATGGTCAATGC-3'; mouse I-FN-β, 5'-TGCTCCTCGTGTTGCGTCCTC-3' and 5'-CATTCTAGATGCTGATATTG-3'; and 5'-CAGCTCAGCAGTTTACACC-3'.

Motif), and anti-GAPDH mouse monoclonal antibody (Biogenesis). The protocols for animal experiments were approved by the Institutional Animal Care and Use Committee of Harvard Medical School.

In Vitro Chemotaxis Assay

In vitro chemotaxis with CXCR3-transfected and untransfected 300-19 cells and conditioned media from LPS-stimulated MΦ with the indicated concentration of adiponectin (24 hours) was placed as described previously.28,29 The chemotaxis index (CI) was defined as the number of cells migrating in response to MΦ-conditioned medium divided by that of cells migrating in response to medium alone.

Cell Transfection and Measurement of Luciferase Activity

A human IP-10 promoter fragment (from −960) subcloned into the firefly luciferase reporter vector pGL3-Basic (Promega) (GL-IP10)20 was transfected into THP-1 cells by the DEAE–dextran sulfate method, as reported previously.27 Equivalent transcriptional efficacy was confirmed by cotransfecting the renilla luciferase control vector, pRL-TK (Promega). After transfection, cells were incubated with RPMI medium 1640 supplemented with 10% FBS for 6 hours and then treated with phorbol 12-myristate 13-acetate at a final concentration of 200 nmol/L for 18 hours to differentiate the THP-1 cells into MΦ-like cells. THP-1 MΦ were treated with the indicated concentration of adiponectin for 24 hours followed by 6 hours of stimulation with or without LPS (5 ng/mL). Luciferase activity was measured with a dual luciferase assay kit (Promega) and a lumimeter.

Immunoblot Analysis

Immunoblot analyses with whole-cell lysates (10 μg/lane) were performed with a standard method using 4% to 12% gradient SDS-PAGE gels (Invitrogen) and nitrocellulose membranes (Amer sham). The following primary antibodies were used for detection with an ECL plus Western Blotting Detection System (Amersham): anti–phospho-specific IFN regulatory factor (IRF)3 (Ser396), anti-STAT1, anti–phospho-specific STAT1(Tyr701), anti-AKT2, anti–phospho-specific ATF2(Thr71), anti–c-Jun, anti–phospho-specific c-Jun(Ser73) (all Cell Signaling Technology), anti-IRF3 (Active Motif), and anti-GAPDH mouse monoclonal antibody (Biogenesis).

Chromatin Immunoprecipitation

After 1 hour of LPS stimulation in human MΦ, chromatin immunoprecipitation (ChIP) assay was performed using the ChIP assay kit (Upstate Biotechnology). Lysates with sonicated chromatin were incubated overnight with 5 μg of rabbit anti-IRF3 antibody (Santa Cruz Biotechnology) or normal rabbit IgG. Precipitated DNA and 10% of sonicated DNA solution used for precipitation (input) as loading controls were amplified by PCR by using the following primers for the IFN-β promoter detection: 5'-TAGTCTATTCATG-AAAACTTTA-3' and 5'-AGTGTTGCTTATTAACTGC-3'. PCR products were separated on 1.5% agarose gel and stained with ethidium bromide.

Mouse Studies

Adiponectin-deficient mice (APN−/−)3 and apolipoprotein E–deficient mice (apoE−/−) (The Jackson Laboratory) were interbred to produce apoE/adiponectin double-deficient mice (apoE−/−APN−/−). Male apoE−/−APN−/− and apoE−/− mice were fed normal chow. At age 30 weeks, plasma samples were collected and thoracic aortae were harvested for histologic analyses or real-time quantitative PCR. Plasma IP-10 levels were measured with the ELISA kit (R&D). In the aortic root, atherosclerotic lesions were measured after staining with oil red O and T lymphocytes were counted after immunostaining with anti-mouse CD4 antibody (BD Pharmingen). RNA isolated from the thoracic aorta was used to quantify the expression levels of CD4 and GAPDH through real-time quantitative PCR. The protocols for animal experiments were approved by the Institutional Animal Care and Use Committee of Harvard Medical School.
Statistical Analysis

Results are shown as means±SEM. Two groups were compared using Student’s t test. Between-group comparison of means was performed by ANOVA, followed by t test. A value of P<0.05 was regarded as a significant difference.

Results

Adiponectin Inhibits LPS-Induced CXCR3 Chemokine Ligand mRNA and Protein Expression in Human MΦ

To unveil potential antiinflammatory pathways mediated by adiponectin in human atherosclerosis, we used cDNA microarrays as screening tools. After 10 days of culture, human monocyte-derived MΦ were treated with or without recombinant human adiponectin (10 μg/mL) for 24 hours and then stimulated with or without LPS for 6 hours. In the initial screen, LPS significantly augmented the expression of 156 of the 38,500 surveyed genes (using a cutoff ratio of LPS versus control of >10.0). Interestingly, adiponectin attenuated the expression of 14 transcripts among the 156 genes (the ratio of APN+LPS versus LPS of less than −10.0). These 14 transcripts included the transcript encoding TNF-α, as previously reported.20-23 IP-10 (CXCL10) emerged as a highly induced transcript in adiponectin in LPS-stimulated MΦ (99.1%; P<0.01 versus LPS alone; n=4; Table I in the online data supplement, available at http://circres.ahajournals.org). Interestingly, Mig (monokine induced by IFN-γ) (CXCL9) and I-TAC (IFN-inducible T-cell α chemotaxtractant) (CXCL11), ligands of CXCR3, also appeared among these 14 mRNAs (97.1%, P<0.05; 90.7%, P<0.01, versus LPS alone, respectively, n=4; supplemental Table I). These 3 chemokines are expressed in MΦ, endothelial cells, and smooth muscle cells in vasculature, and they recruit T-lymphocyte migration, an important feature in the development of atheromata.30-32

To validate the cDNA microarray data, real-time quantitative PCR tested the concentration-dependent effect of adiponectin on chemokine expression in LPS-stimulated human MΦ. Adiponectin suppressed the expression of LPS-induced IP-10, Mig, and I-TAC in a concentration-dependent manner (Figure 1A). IFN-γ in MΦ, vascular endothelial cells, and smooth muscle cells induces the chemokines IP-10, Mig, and I-TAC.31 Therefore, we also tested the gene expression of this trio of chemokines stimulated by IFN-γ in adiponectin-pretreated human MΦ. However, in contrast to LPS stimulation, adiponectin did not influence the expression levels of these genes in MΦ stimulated with IFN-γ (Figure 1B).

Concordant with suppression of mRNA levels, adiponectin reduced the release of IP-10 protein from LPS-stimulated MΦ in a concentration-dependent manner (Figure 2).

Adiponectin Inhibits CXCR3-Dependent Chemotactic Activity Released From LPS-Stimulated Human MΦ

To evaluate the functional consequences of inhibition by adiponectin of LPS-induced CXCR3 chemokine ligands in human MΦ, we assayed chemotaxis in vitro using CXCR3-transfected lymphocytes and supernatants from cultured MΦ. Cell-free supernatants from LPS-stimulated MΦ contained substantial chemotactic activity for CXCR3 300-19 lymphocytes (CI=7.46) compared with supernatants collected from untreated MΦ (CI=1) (Figure 3). Adiponectin reduced the CXCR3 chemotactic activity in LPS-stimulated MΦ up to 82% at 10 μg/mL adiponectin compared with no pretreatment (CI=1.37, P<0.001; n=4; Figure 3). The same supernatants did not attract untransfected 300-19 cells (Figure 3), indicating that adiponectin specifically inhibited the CXCR3 chemotactic activity.

Adiponectin Inhibits LPS-Induced IP-10 Promoter Activity

To characterize further the underlying mechanisms for the effect of adiponectin on IP-10 transcription, we transiently
Adiponectin Does Not Change IP-10 mRNA Stability in Human Macrophages

To probe the mechanism by which adiponectin inhibits accumulation of CXCR3 chemokine ligand mRNA, we further examined the effect of adiponectin on IP-10 mRNA degradation. Adiponectin (10 μg/mL) did not change the level of IP-10 mRNA remaining in human MΦs stimulated with LPS after actinomycin D treatment for 1 and 4 hours (Figure 4B).

Adiponectin Suppresses IP-10 Through the Inhibition of IFN-β

LPS stimulation in MΦ can induce an early release of IFN-β, followed by an increase of IFN-inducible genes such as IP-10.33 To investigate the inhibitory mechanism of LPS-induced IP-10 by adiponectin, we measured levels of mRNAs encoding IFN-β or IP-10 following 0, 1, 2, 4, and 6 hours of LPS stimulation. In LPS-stimulated MΦ, the expression of IFN-β mRNA increased within 1 to 2 hours after LPS stimulation (Figure 5A), and the increase of IP-10 mRNA started at 2 hours after LPS stimulation and continued to rise at later time points (Figure 5B). Adiponectin strongly inhibited the early IFN-β mRNA increase in LPS-stimulated MΦ in a concentration-dependent manner (Figure 5A and 5C).

Adiponectin treatment also suppressed IP-10 mRNA expression in LPS-stimulated MΦ at later time points (Figure 5B) in a concentration-dependent manner (Figure 1A).

In an autocrine/paracrine fashion, LPS-induced IFN-β in MΦ activates a secondary wave of IFN-inducible gene transcription, largely through the activation of the transcription factor STAT1.34 Therefore, we examined the effect of adiponectin pretreatment on STAT1 activation in LPS-stimulated MΦ by immunoblot. STAT1 phosphorylation of MΦ occurred between 2 and 4 hours after LPS stimulation, markedly attenuated by adiponectin (Figure 6A). On the other hand, in IFN-β-stimulated MΦ, the phosphorylation of STAT1 started 1 hour after stimulation probably because IFN-β directly bound to IFN-β receptor. However, adiponectin did not affect the phosphorylation of STAT1 after IFN-β stimulation (Figure 6B). These data imply that the suppressive effect of adiponectin on IP-10 expression does not depend on inhibition of downstream signaling of IFN-β receptor but mainly by the reduced IFN-β production.

Adiponectin Suppresses Phosphorylation of IRF3 and Subsequent IRF3 Binding to IFN-β Promoter

In LPS-stimulated MΦ, the expression of IFN-β requires the activation of transcription factor IRF3, a major transcriptional factor in the regulation of IFN-β, as well as NF-κB, c-Jun,

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Figure 3. Adiponectin lowers CXCR3-dependent chemotactic activity released from LPS-stimulated human MΦ. Human MΦ were treated with the indicated concentration of adiponectin for 24 hours, followed by LPS (5 ng/mL) for 24 hours. Cell-free MΦ supernatants were tested in an in vitro chemotaxis assay using CXCR3-transfected 300-19 lymphocytes or parental untransfected cells for 5 hours. The numbers of migrated cells were determined and defined as chemotaxis index (CI), as described in Materials and Methods. Data represent means ± SEM of CI (n = 4). †P < 0.001 vs LPS-stimulated CXCR3-transfected cells.

Figure 4. Adiponectin inhibits IP-10 promoter activity but does not affect IP-10 mRNA stability. A, THP-1 monocytoid cells were transfected with IP-10 promoter construct and differentiated into macrophage-like cells as described in Materials and Methods. The cells were incubated with the indicated concentration of adiponectin for 24 hours, then further maintained with or without LPS for 6 hours (5 ng/mL). Luciferase assays were performed according to the protocol of the supplier. TK indicates control vector (pRL-TK) (n = 4). *P < 0.05, †P < 0.01, ‡P < 0.001 vs LPS. B, Human MΦ pretreated with or without adiponectin (10 μg/mL) for 24 hours were stimulated with LPS (5 ng/mL), and actinomycin D (final concentration, 5 μg/mL) was added to each sample 3 hours later. RNA was harvested at 0, 1, and 4 hours after adding actinomycin D, and IP-10 mRNA levels were quantified with real-time RT-PCR. Data are expressed relative to the values at time 0 hour in means ± SEM (n = 3).
Apocrine c-Jun or ATF2 after stimulation with LPS (Figure 7C).

NF-kB pretreatment suppressed the phosphorylation of IRF3 at 1 and 2 hours after stimulation with LPS as shown by immunoblotting (Figure 7A). Moreover, ChIP analysis revealed that adiponectin suppressed the specific binding of activated IRF3 to IFN-β promoter in LPS-stimulated MΦ (Figure 7B). As previously reported, adiponectin suppressed the activation of NF-κB in LPS-stimulated MΦ (data not shown). Adiponectin pretreatment also mildly attenuated the phosphorylation of c-Jun or ATF2 after stimulation with LPS (Figure 7C).

Adiponectin Deficiency Promotes Atherosclerosis and Increases Plasma IP-10 Levels In Vivo

At age 30 weeks, plasma IP-10 levels in apoE−/− APN−/− mice were 44% higher than in apoE−/− APN+/− mice (32.2±1.6 pg/mL vs 46.6±5.8 pg/mL, P<0.05, n=8 each; Figure 8A). The 2 groups exhibited no difference in body weight, total cholesterol, triglycerides, and glucose (data not shown). We found that the apoE−/− APN−/− (n=7) mice developed 61% larger atherosclerotic lesions in the aortic root compared with apoE−/− APN+/− mice (n=6) (0.18±0.03 versus 0.29±0.03 mm², P<0.05; Figure 8B). ApoE−/− APN−/− (n=7) mice accumulated 63% more T lymphocytes immunostained with anti-mouse CD4 antibody compared with apoE−/− APN+/− mice (n=6) (7.8±1.0 versus 12.7±1.4 CD4 positive cells/section, P<0.05; Figure 8C, left). The results of quantitative RT-PCR verified this increased accumulation of CD4-stained T lymphocytes, showing apoE−/− APN−/− mice had 104% more CD4 mRNA expression in the thoracic aorta than did apoE−/− APN+/− mice (100.0±0.08 versus 204.4±0.13%, P<0.0001, n=7 each; Figure 8C, right).

Discussion

MΦ participate pivotally in the pathogenesis of atherosclerosis and also contribute to inflammation and insulin resistance associated with excess adipose tissue. The current study probed a new property of adiponectin as a strong inhibitor of CXCR3 chemokine ligands IP-10, Mig, and I-TAC in LPS-stimulated MΦ and as a regulator of T-lymphocyte chemotraction. T lymphocytes critically regulate the development of certain arterial diseases, eg, atherosclerosis, allograft arteriopathy. Our in vivo study revealed that adiponectin deficiency accelerated the development of atherosclerosis, promoted the accumulation of T lymphocytes, and increased plasma levels of IP-10.

Both IFN-γ and LPS can induce these 3 chemokines in MΦ. However, our data showed that adiponectin limits expression of these chemokines after LPS but not IFN-γ stimulation. These observations indicate that adiponectin acts at the level of the signaling pathway of Toll-like receptor (TLR)4 but not of IFN-γ receptor-1 and -2. Although the lower concentration of adiponectin (0.1 μg/mL) suppressed mRNA expression of these chemokines to some degree in LPS-stimulated MΦ, the higher concentrations compatible with physiological plasma levels in humans (1, 3, and 10 μg/mL) displayed stronger suppression in a concentration-dependent manner. Moreover, only the physiological concentration of adiponectin suppressed IP-10 protein secretion and CXCR3 chemotactic activity in LPS-stimulated MΦ supernatant in a concentration-dependent manner. Therefore, effective suppression of these chemokines requires the higher, physiological concentration of adiponectin.

Adiponectin significantly suppressed LPS-induced IP-10 promoter activation in THP-1 cells, although adiponectin
suppresses LPS-induced IP-10 promoter to a lesser extent than IP-10 mRNA. This discrepancy may result from the cell type–specific differences between the THP-1 cell line and human primary macrophages, the transfection efficiency of IP-10 promoter, or the possibility that additional upstream promoter elements may be required to recapitulate endogenous IP-10 responsiveness in THP-1 cells. On the other hand, adiponectin did not change IP-10 mRNA stability in LPS-stimulated MΦ. These observations indicate that adiponectin regulates IP-10 mRNA expression at the transcriptional level.

LPS induces a variety of proinflammatory genes by activating 2 major pathways of TLR4: MyD88-dependent and -independent pathways. The MyD88-independent pathway activates IRF3 and the induction of IFN-β. IFN-β, in turn, stimulates STAT1, augmenting the expression of IFN-inducible genes including IP-10. Adiponectin almost completely abolished IFN-β expression and subsequent IP-10 induction. Moreover, immunoblot analyses showed that adiponectin reduced activation of STAT1 in LPS-stimulated MΦ but did not in IFN-β-stimulated MΦ. These results indicate that adiponectin suppresses IP-10 through the inhibition of IFN-β but not directly by the attenuation of STAT1 activation.

We also investigated the effect of adiponectin on downstream signaling of TLR4. According to microarray data, adiponectin did not attenuate all genes induced by LPS stimulation, such as CCL20 (data not shown), suggesting that adiponectin does not interfere with the binding of LPS to TLR4 but regulates the post–receptor signaling of TLR4. In the MyD88-dependent pathway, LPS ligation facilitates activation of NF-κB as well as c-Jun N-terminal kinase and p38 kinases that subsequently activate c-Jun and ATF2, respectively. Previous studies reported that adiponectin attenuates NF-κB activation in TNF-α–stimulated human endothelial cells and LPS-stimulated pig MΦ. In accordance with these findings, adiponectin inhibited activation of NF-κB as well as c-Jun and ATF2.

In the MyD88-independent pathway, activation of transcription factor IRF3 plays a pivotal role in the induction of IFN-β.
IFN-β. Immunoblot and ChIP analyses documented that adiponectin attenuates IRF3 phosphorylation and the subsequent binding of IRF3 to the IFN-β promoter. Interestingly, our findings point to attenuation by adiponectin of TLR4 signaling by both the MyD88-dependent and -independent pathways.33 Recent studies implicate TLR4 signaling in the development of cardiovascular diseases and insulin resistance.57,58 Because of the intimate involvement of adiponectin in obesity and in the metabolic syndrome, further studies to elucidate the precise inhibitory mechanisms of adiponectin on TLR4 signaling may indicate new therapeutic strategies as well as help unravel the pathogenesis of these conditions.

This study affirms that adiponectin serves as an antiatherogenic adipocytokine and discloses a novel mechanism: regulation of T-lymphocyte–active CXCR3 chemokine ligands and T-lymphocyte migration. Our findings illustrate a here-tofore apparent link between dysmetabolism in obesity and adaptive immunity. T lymphocytes participate importantly in atherogenesis. The present results suggest that adiponectin can mitigate atheroma formation and evolution through attenuation of T cell recruitment and may thus act as an endogenous inhibitor of adaptive immunity.

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Disclosures

None.

References


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cDNA microarray screening shows that CXCR3 ligand chemokines are target of adiponectin

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Numbers represent the folds changes between two indicated conditions by cDNA microarray analysis (mean value of four independent donors)