Peroxisome proliferator–activated receptors (PPARs) are members of the superfamily of nuclear hormone receptors.1–3 Members of this family include PPARα, PPARβ, and PPARγ. PPARs are characterized by distinct tissue distribution patterns and metabolic functions. PPARα is expressed preferentially in tissues exhibiting high catabolic rates of fatty acids, such as liver and brown adipose tissue, and plays a key role in lipid metabolism.4,5 PPARβ (also called NUC-1 or PPARδ) is ubiquitously expressed, and its specific function is still unknown.5,6 PPARγ is adipocyte tissue selective and is implicated as a mediator of adipocyte differentiation and regulation of glucose homeostasis.7,8 The activity of PPARs is regulated by various agents, including insulin, fatty acids, fibrates, leukotriene B4, prostaglandin J2, and synthetic thiazolidinedione drugs.9–13 PPARs function as ligand-dependent transcription factors, which, on heterodimerization with the 9-cis-retinoic acid receptor, bind to a specific response element termed peroxisome proliferator responsive element (PPRE), which is present in the promoter of various genes implicated in lipid metabolism, such as lipoprotein lipase (LPL).14,15

Recent findings demonstrate that PPARs are involved in several metabolic diseases, such as obesity, dyslipidemia, atherosclerosis, and diabetes. Diabetes is a major risk factor for atherosclerosis.16 Accumulating evidence indicates that immune mechanisms play a critical role in the pathogenesis of atherosclerosis. Arguments that point to the monocyte/macrophage as a principal participant in atherogenesis include its role in arterial lipid metabolism and as a precursor of foam cells.17–20 Recent studies have demonstrated that PPARs are expressed in cells of the monocyte/macrophage lineage21 and in macrophage-derived foam cells of atherosclerotic lesions.22–24 It has been proposed that PPARs may regulate macrophage activation and lipid metabolism in mononuclear cells.22,24–27

Although macrophage PPARs may play a key role in the accelerated atherosclerosis associated with diabetes, the mod-
glutamyl dehydropyranose, and treated with glyburide and metformin. None of the patients were excluded from the study.

**Methods**

**Reagents**

FCS was purchased from Hyclone Laboratories, DMEM was obtained from ICN Biochemicals Inc. RPMI 1640 medium, Hanks’ balanced salt solution, and Trizol reagent were purchased from Gibco-BRL. Lymphoprep and penicillin-streptomycin were obtained from Nycomed Pharma As and Flow, respectively. D-Glucose, RPMI 1640 medium, Hanks’ balanced salt solution, and FCS were purchased from Hyclone Laboratories. DMEM was obtained from ICN Biochemicals Inc.

**Human and Murine Macrophages**

Human monocytes were isolated as previously described. Peripheral blood mononuclear cells were isolated by density centrifugation with Ficoll, allowed to aggregate in the presence of FCS, and then further purified by the rosetting technique. After density centrifugation, highly purified monocytes (85% to 90%) were recovered, as assessed by flow cytometry (FACSscan, Becton Dickinson). Differentiation of monocytes into macrophages was achieved by culturing the freshly isolated monocytes in RPMI 1640 medium (2000 000/mL) containing 20% (vol/vol) autologous serum for 4 days.

The J774 murine macrophage cell line was obtained from American Type Culture Collection (ATCC). Murine macrophages were cultured in DMEM containing 10% FCS and 100 μg/mL penicillin-streptomycin (FCS-DMEM). For experiments assessing the effect of increasing concentrations of glucose, a customized preparation of FCS-DMEM was used; this preparation contained 5.6 mmol/L of glucose to which varying amounts of glucose were added to make up the desired final glucose concentrations.

**Patients**

The study group consisted of 7 patients with type 2 diabetes and 7 healthy control subjects. They gave written consent to participate in this study, which was approved by the Center Hospitalier de l’Université de Montréal Research and Ethics committees. All patients recruited from our outpatient clinic were normotriglyceridemic and treated with glyburide and metformin. None of the patients was primarily insulin dependent. Characteristics of the study population are presented in Table 1. Healthy controls, matched with patients for sex, age, and body mass index, were recruited from the hospital staff and relatives. Subjects with infectious or inflammatory conditions or with cardiac, renal, or pulmonary decompensated diseases or who were treated with anti-inflammatory or antioxidant drugs were excluded from the study.

**Analysis of PPAR mRNA Expression**

The levels of PPAR mRNAs in human and murine macrophages were assessed by semiquantitative polymerase chain reaction (PCR) and Northern blot analysis, respectively.

**Northern Blot Analysis**

Ten million J774 macrophages were plated in plastic Petri dishes (100×20 mm, Falcon). After treatment with appropriate agents, macrophages were lysed with guanidine isothiocyanate. Total RNA was purified by centrifugation through a cesium chloride gradient. Total RNA (20 μg) was separated on a 1.2% agarose gel containing 2.2 mol/L formaldehyde. The blots were prehybridized for 8 hours. The mRNA expression was analyzed by hybridization with [32P]dCTP (specific activity 3000 Ci/mmol, Amersham)–labeled murine PPARα, PPARβ, PPARγ, and GAPDH. Primers (sense and antisense) used in the PCR reaction were shown in Table 2. A 510-bp human PPARα cDNA fragment, a 406-bp murine PPARβ cDNA fragment, a 421-bp murine PPARγ cDNA fragment, and a 456-bp human GAPDH cDNA fragment were amplified enzymatically by repeated cycles. An aliquot of each reaction mixture was then subjected to electrophoresis on 1% agarose gel. The intensity of the bands was measured by an image analysis scanning system (Alpha Imager 2000, Packard Instrument Co).

**Analysis of PPAR Protein Expression**

After appropriate treatments, murine macrophages were pelleted and lysed in 50 mmol/L Tris HCl (pH 7.4), 150 mmol/L NaCl, and 1% Nonidet P-40. The cell lysates were subjected to electrophoresis on 8% sodium dodecyl sulfate–polyacrylamide gel. After transfer to nitrocellulose membranes, the blots were probed with antibodies to PPARα and PPARγ. The bands were visualized using the enhanced chemiluminescence technique (Amersham).

**Results**

Increased glucose concentrations up-regulated PPARα expression in murine peritoneal macrophages, whereas PPARγ expression was not affected (data not shown). In human monocytes, glucose concentrations up-regulated both PPARα and PPARγ expression (Figures 1 and 2).

**Discussion**

Glucose is an important regulator of lipid metabolism in human and murine macrophages. In the present study, we determined the in vitro effect of high glucose concentration on macrophage PPAR expression and examined the regulation of macrophage PPAR expression in human type 2 diabetes. In addition, on the basis of previous results demonstrating a stimulatory effect of glucose on macrophage PPAR expression and a key role of PPARs in the control of LPL gene expression,4,15 we also investigated the role of PPARs in the regulation of macrophage LPL mRNA expression by glucose.

**Table 1. Characteristics of the Study Population**

<table>
<thead>
<tr>
<th></th>
<th>Patients With Type 2 Diabetes</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50.4±4.5</td>
<td>42.6±4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.9±2.8</td>
<td>27.1±1.2</td>
<td>NS</td>
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<tr>
<td>Fasting glucose, mmol/L</td>
<td>7.9±0.9</td>
<td>4.9±0.1</td>
<td>&lt;0.005</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.79±0.34</td>
<td>1.01±0.01</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.19±0.36</td>
<td>4.34±0.18</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.23±0.10</td>
<td>1.44±0.11</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.24±0.26</td>
<td>2.69±0.21</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. NS indicates not significant.

**Table 2. Sequences of Oligonucleotides**

<table>
<thead>
<tr>
<th></th>
<th>Murine PPARα</th>
<th>Murine PPARβ</th>
<th>Murine PPARγ</th>
<th>Human PPARα</th>
<th>Human GAPDH</th>
<th>PPRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense</td>
<td>5’-GTGGTGCTATTG/GGGCATACGTGAC-3’</td>
<td>5’-ATACGGGTCATGTTCTACGC-3’</td>
<td>5’-CTGCTCTGATGTGCTACCTG-3’</td>
<td>5’-GTGGAGCTGACATGACTAC-3’</td>
<td>5’-ATACAGTGTCCTCATATCAT-3’</td>
<td>5’-GAGAAGGGGGAAGAGAGA-3’</td>
</tr>
<tr>
<td>Antisense</td>
<td>3’-CGTCTGATGCTACGTGAC-5’</td>
<td>3’-GACAGGAGCAGCTGACCT-5’</td>
<td>3’-ATACAGTGTCCTCATATCAT-3’</td>
<td>3’-GTGGAGCTGACATGACTAC-3’</td>
<td>3’-ATACAGTGTCCTCATATCAT-3’</td>
<td>3’-GAGAAGGGGGAAGAGAGA-3’</td>
</tr>
</tbody>
</table>

**Institutional Review Board Approval**

This study was approved by the Ethics Committee of the Centre Hospitalier de l’Université de Montréal Research and Ethics Committee. All patients gave informed consent prior to participation.

**Acknowledgments**

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Nonidet P-40. Samples were centrifuged at 13,000 rpm for 15 minutes at 4°C, and supernatants were collected. Protein concentrations were determined with a colorimetric assay (Bio-Rad) by use of BSA as a standard. Samples (50 μg proteins) were applied to 10% SDS-polyacrylamide gel and transferred to a nitrocellulose membrane by using a Bio-Rad transfer blotting system at 100 V for 60 minutes. Membranes were blocked overnight at 4°C with a solution of PBS–0.3% Tween 20 containing 1% BSA and 5% FCS. After a wash with PBS–0.05% Tween 20, membranes were incubated for 3 hours at room temperature with anti-PPARα antibody (1/1000; kindly provided by Dr W. Wahli, Université de Lausanne, Lausanne, Switzerland) in PBS–0.05% Tween 20 and FCS 1%. After a further wash, membranes were incubated with IgG antibodies linked to the horseradish peroxidase in PBS–0.05% Tween 20 and FCS 5% for 1 hour at room temperature. Membranes were washed with PBS containing 0.05% Tween 20. Antigen detection was performed with an enhanced chemiluminescence detection system (Amersham).

DNA Binding Assay

The isolation of nuclei was performed as previously described. Briefly, 5×10⁶ J774 cells were collected, washed with cold PBS, and lysed in 1 mL of ice-cold buffer A (15 mmol/L KCl, 2 mmol/L MgCl₂, 10 mmol/L HEPES, 0.1% phenylmethylsulfonyl fluoride, and 0.5% Nonidet P-40). After a 10-minute incubation on ice, lysed cells were centrifuged, and the nuclei were washed with buffer A without Nonidet P-40. The nuclei were then lysed in a buffer containing 2 mmol/L KCl, 25 mmol/L HEPES, 0.1 mmol/L EDTA, and 1 mmol/L dithiothreitol. After a 15-minute incubation period, a dialysis buffer (25 mmol/L HEPES, 1 mmol/L dithiothreitol, 0.1% phenylmethylsulfonyl fluoride, 2 μg/mL aprotinin, 0.1 mmol/L EDTA, and 11% glycerol) was added to the nuclei preparation. Nuclei were collected by centrifugation for 20 minutes at 13,000 rpm. Aliquots (50 μL) of the supernatants were frozen at −70°C, and protein concentration was determined. DNA retardation (mobility shift) electrophoresis assays were performed as previously described by Fried and Crothers. Briefly, 5 μg nuclear extracts were incubated for 15 minutes in the presence of 5× binding buffer (125 mmol/L HEPES, pH 7.5, 50% glycerol, 250 mmol/L NaCl, 0.25% Nonidet P-40, and 5 mmol/L dithiothreitol) in the presence or absence of 200 ng anti-PPARα, anti-PPARβ (kindly provided by Dr W. Wahli, Université de Lausanne, Lausanne, Switzerland), or anti-PPARγ (Calbiochem) antibodies. End-labeled double-stranded consensus sequences of the LPL promoter PPAR-enhancing element (20 000 cpm per sample) were then added to the samples for 30 minutes. Samples were analyzed on a 4% nondenaturing polyacrylamide gel containing 0.01% Nonidet P-40. The specificity of the nuclear protein binding was assessed by incubating the nuclear proteins isolated from murine macrophages with labeled DNA probe in the presence of a 1000-molar excess of unlabeled DNA probe.

DNA Probes

The cDNA probe for detection of murine PPARα was prepared by PCR. cDNA was obtained from total RNA by using a reverse transcription reaction. Two synthetic primers (Table 2) spanning the region of the PPARα probe. The PPARα probe was purified by Sephaglas BandPrep Kit (Pharmacia). The cDNA probe for murine S28 was purchased from ATCC. A 29-mer double-stranded oligonucleotide (Table 2) containing the consensus sequence for the PPRE of the human LPL gene promoter was synthesized with the aid of an automated DNA synthesizer. After annealing, the double-stranded oligonucleotide was labeled with [γ-32P]ATP by using the Boehringer-Mannheim 5’ end-labeling kit.

Statistical Analysis

All values were expressed as the mean±SEM. For single comparisons, data were analyzed by the Student t test or Mann-Whitney rank sum test. For multiple comparisons, data were analyzed by ANOVA, followed by the Tukey test or the Dunn test.

Results

Effect of High Glucose Concentrations on Human Monocyte-Derived Macrophage PPARα, PPARβ, and PPARγ mRNA Levels

To evaluate the effects of high glucose concentrations on macrophage PPAR mRNA expression, monocyte-derived macrophages obtained from healthy control subjects were cultured for 48 hours in the presence of 5.6 or 30 mmol/L glucose. After 2 days, cells were lysed. A, PPARα, PPARβ, PPARγ, and GAPDH mRNA expression was analyzed by PCR. B, PPARα, PPARβ, and PPARγ mRNA levels were normalized to the levels of GAPDH mRNA. Data represent the mean±SEM of 4 different experiments. *P<0.05, **P<0.02, and ***P<0.001 vs control.

Regulation of Monocyte-Derived Macrophage PPAR mRNA Expression in Patients With Type 2 Diabetes

To investigate the regulation of macrophage PPARs in diabetes, PPAR mRNA expression was determined in monocyte-derived macrophages isolated from patients with type 2 diabetes. Macrophages of diabetic patients expressed higher PPARα and PPARβ mRNA levels than did macrophages of control subjects (PPARα mRNA levels [fold increase over control values], 1.93±0.16, P=0.003; PPARβ
mRNA levels [fold increase over control values], 1.92 ± 0.35, P = 0.048; Figure 2A and 2B). Macrophages of diabetic patients also expressed significantly lower PPARγ mRNA levels compared with levels in macrophages of control subjects (PPARγ mRNA levels [fold decrease under control values], 1.31 ± 0.11, P = 0.026; Figure 2C).

Role of PPARs in Upregulation of Macrophage LPL Gene Expression in Response to Glucose

On the basis of our previous observations that LPL, a key target gene for PPARs, is upregulated by glucose in J774 murine macrophages, we next determined whether incubation of J774 cells in the presence of high glucose concentrations might induce changes at the level of the LPL gene promoter binding PPAR protein.

As part of a setup for subsequent gel-shift data, PPARα mRNA and protein levels in J774 cells exposed to high glucose concentrations were first determined. Incubation of J774 cells with increasing glucose concentrations (5.6, 10, 20, and 30 mmol/L) for 48 hours increased, in a dose-dependent manner, PPARα mRNA expression by these cells (Figure 3A). Under these experimental conditions, no modulation of the mRNA expression of S28, used as an internal control, was observed (Figure 3B). PPARα mRNA levels normalized to the levels of S28 mRNA are illustrated in Figure 3C.

Determination of PPARα protein levels in J774 cells exposed for 48 hours in the presence of 30 mmol/L glucose demonstrated a significant increase in the expression levels of this receptor over control values (PPARα protein levels [fold increase over control values] for 30 mmol/L glucose, 2.95 ± 0.43; Figure 4).

Exposure of J774 cells to a high glucose environment for 60 hours resulted in a significant increase in the binding of nuclear proteins to the PPRE consensus sequence of the LPL promoter (Figure 5). The specificity of these proteins is demonstrated by the fact that they were effectively competed by excess unlabeled PPRE oligonucleotide. In the glucose-treated nuclear extracts, antibodies against PPARα and PPARβ decreased the binding activity to the PPRE sequence, whereas anti-PPARγ antibody was ineffective (Figure 5).

Discussion

Glucose is the primary metabolic substrate of macrophages. Enhanced glucose metabolism occurs in these cells in response to mitogenic or immunologic stimulation. Evidence has been provided that high glucose regulates in vitro macrophage lipid metabolism and function. Indeed, it has
be shown that macrophages cultured in a high glucose environment overexpress LPL, a key enzyme in the catabolism of triglyceride-rich lipoproteins, and secrete large amounts of various proinflammatory cytokines, including tumor necrosis factor-α and interleukin-6.

PPARs are key nuclear factors in nutrient gene interaction that translate nutritional signals into changes in the expression of genes implicated in lipid and glucose metabolism. In adipose tissue, skeletal muscle, and hepatic cells, PPAR mRNA expression has been shown to be under hormonal control, as reflected by the induction at the transcriptional level of PPARα and PPARγ gene expression by insulin and glucocorticoids. The observation that PPARs are transcriptionally active in human macrophages has raised the question of the nature of the regulators of PPAR mRNA expression and the target genes for PPARs in these cells. Insight into the regulation of PPARγ expression in activated macrophages has recently been provided by Ricote et al, who demonstrated an induction of PPARγ expression in these cells by colony-stimulating factor, granulocyte/macrophage colony–stimulating factor, and oxidized LDL.

The present study demonstrates for the first time that high glucose levels regulate PPAR expression in human macrophages; PPARα and PPARβ are increased, whereas PPARγ is decreased. These results identify the macrophage PPAR genes as response genes for glucose action. The molecular mechanism(s) by which glucose upregulates macrophage PPARα and PPARβ mRNA levels is presently unknown. One may hypothesize that such an effect may result from the direct interaction of glucose with a putative glucose responsive element present in the promoter of these genes. DNA motifs that could mediate glucose responsiveness of genes include the cis-acting carbohydrate responsive element (5‘-CAGCGGTNNNGCG-3′), the CAGCGG motif related to the consensus sequence binding site for the c-myc family of transcription factors, and other glucose responsive elements, such as the stimulatory protein 1 sites.

The presence of a stimulatory protein 1 site (−130 to −125) and of sequences similar to the cis-acting carbohydrate responsive element (−313 to −302) and the CAGCGG motif (−869 to −862 and −140 to −135) in the promoter of the PPARα gene suggests that glucose may induce PPARα gene expression through this site(s). Our preliminary results (data not shown) showing that high glucose increases the level of binding of nuclear proteins to stimulatory protein 1 and carbohydrate responsive elements present in the PPARα promoter seem to support this possibility. Alternatively, intracellular accumulation of fatty acids resulting from glucose interaction with lipid metabolism may be responsible for PPARα gene induction. This possibility is supported by one recent study demonstrating, in hepatic cells, an upregulatory effect of fatty acids on the steady-state PPAR mRNA levels.

Negative regulation of PPARγ gene expression in glucose-treated macrophages could theoretically involve tumor necrosis factor-α. Indeed, it has been shown that high glucose stimulates macrophage tumor necrosis factor-α secretion and that this cytokine, in turn, exerts a suppressive effect on PPARγ mRNA expression.

Because PPARs regulate lipid metabolism, genes involved in macrophage lipid metabolism, such as LPL, are likely candidates as target genes for PPARs in these cells. This view is supported by the observation that PPAR agonists increase LPL gene expression and by the demonstration of a PPRE site in the regulatory sequence of the human LPL gene. The parallel induction of PPARα and LPL gene expression in glucose-treated macrophages is consistent with the view that the transcriptional effect of glucose on macrophage LPL that we previously reported may involve this PPAR isoform. This possibility is further supported by the fact that anti-PPARα decreases the enhanced binding of nuclear proteins isolated from glucose-treated macrophages.

**Figure 5.** Effect of high glucose concentration on the binding activity of nuclear proteins extracted from murine macrophages to the regulatory PPRE sequence of the human LPL gene promoter. Murine macrophages were exposed for 60 hours to 5.6 or 30 mmol/L glucose. The nuclear proteins isolated from these cells were incubated with double-stranded PPAR regulatory element of the LPL gene. Retardation was assessed on a 4% non-denaturing polyacrylamide gel. Data represent the results of one of 3 representative experiments. Lanes are as follows: lane 1, 5.6 mmol/L glucose; lane 2, 30 mmol/L glucose; lane 3, 30 mmol/L glucose + competitor; lane 4, 30 mmol/L glucose + anti-PPARα antibody; lane 5, 30 mmol/L glucose + anti-PPARβ antibody; and lane 6, 30 mmol/L glucose + anti-PPARγ antibody.
to the PPRE regulatory domain of the LPL gene. The upregulation of PPARβ by high glucose also suggests a potential role of this isoform in the stimulation of LPL gene expression by glucose. Our finding that anti-PPARβ antibody decreases the glucose-induced binding activity to the PPRE is consistent with this view. Finally, despite the reduction of PPARγ expression by glucose, it cannot be excluded that induction of a potent PPARγ ligand by glucose may be sufficient to activate this isoform and thereby stimulate the LPL target gene. However, this possibility is not supported by our results, which show that anti-PPARγ antibody does not decrease the glucose-induced binding activity to the PPRE regulatory domain of the LPL gene.

Genes involved in the control of inflammation may represent additional targets for PPARs in macrophages. Indeed, it has been previously shown that mice rendered deficient for PPARα display a prolonged response to inflammatory stimuli11 and that PPARγ negatively regulates genes implicated in macrophage activation.25,26 On the basis of these results and observations that glucose-treated macrophages exhibit an increase in cytokine production37,38 and an inhibition of different subcellular localizations of PPARγ, that PPARγ negatively regulates genes implicated in macrophage activation, it is tempting to speculate that the stimulatory effect of glucose on macrophage function may involve, at least partly, a suppression of PPARγ activation in these cells. Whether PPARα and PPARγ exert differential effects on macrophage function and whether the different subcellular localizations of PPARα and PPARγ proteins in macrophages, i.e., PPARγ in the nucleus and PPARα in the cytoplasmic compartment,27 are responsible for these effects remain to be investigated.

Human diabetes is associated with a high incidence of atherosclerosis.16 Recent evidence demonstrates that PPARγ is expressed in macrophage foam cells of human atherosclerotic lesions.22–24 Furthermore, expression of PPARα, PPARβ, and PPARγ has been documented in vascular cells, including macrophages, smooth muscle cells,52,53 and endothelial cells.54 PPARs may interfere with atherogenesis by regulating arterial lipid metabolism and/or inflammation. Our findings that human type 2 diabetes is associated with altered macrophage PPAR gene expression further suggest that changes in macrophage PPAR activation may occur in the vascular wall in the hyperglycemic state and may influence atherogenesis. Dysregulation of macrophage PPARs in the arterial wall may contribute, by increasing the intra macrophage production of LPL and of proinflammatory cytokines, to the accelerated atherosclerosis associated with diabetes. Given the potential proatherogenic effect of macrophage LPL in the arterial wall, study of the biological role of PPAR expression and induction of a potent PPARγ ligand by glucose may be sufficient to activate this isoform and thereby stimulate the LPL target gene. However, this possibility is not supported by our results, which show that anti-PPARγ antibody does not decrease the glucose-induced binding activity to the PPRE regulatory domain of the LPL gene.

Acknowledgments
This study was supported by grants from the Medical Research Council of Canada, the Heart and Stroke Foundation of Canada, and the Association Diabète Québec. The authors thank Dr W. Wahli (Université de Lausanne, Lausanne, Switzerland) for providing the anti-PPARα and anti-PPARβ antibodies and Dr O. Serri (University of Montreal, Metabolic Unit of Notre-Dame Hospital, Montreal, Quebec, Canada) for the referral of the diabetic patients and for his helpful comments in the preparation of the manuscript.

References
Differential Regulation of Macrophage Peroxisome Proliferator–Activated Receptor Expression by Glucose: Role of Peroxisome Proliferator–Activated Receptors in Lipoprotein Lipase Gene Expression
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