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High glucose stimulates macrophage SR-BI expression and induces a switch in its activity from cholesterol efflux to cholesterol influx

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ABSTRACT

Aims: Diabetes is associated with atherogenesis and macrophage-foam cell formation, due in part to a decrease in HDL-mediated cholesterol efflux from macrophages. This study examined the expression of proteins involved in cholesterol transport, i.e. ABCA1 and SR-BI, under diabetic conditions.
Methods and results: ABCA1 expression was similar, whereas SR-BI expression (mRNA and protein) was significantly increased in mouse peritoneal macrophages (MPM) harvested from C57Bl/6 diabetic mice, compared to MPM from control non-diabetic mice. Similar results were obtained in vitro in J-774A.1 macrophage-like cell line incubated with high (30 mM) vs. low (5 mM) glucose concentrations. Accordingly, association and internalization of HDL to MPM from diabetic mice, or to J-774A.1 macrophages grown under diabetic conditions was significantly higher compared to control cells. Unexpectedly, however, increased macrophage SR-BI expression was associated with a substantial reduction in HDL-mediated cholesterol efflux from the macrophages. Moreover, total cellular cholesterol content was increased by 28% in macrophages incubated with HDL under high glucose concentrations, compared to low glucose concentrations. This effect was abolished by a rabbit polyclonal anti-SR-BI, which blocks binding to the receptor, or alternatively by using BLT1, a specific inhibitor of lipid transport via the SR-BI.
Conclusions: Diabetes stimulates the expression of SR-BI in macrophages and leads to a shift in its activity from HDL-mediated cholesterol efflux to HDL-mediated cholesterol influx. These effects may lead to increased foam cell formation and atherosclerosis development.

Introduction

Diabetes mellitus is associated with an increased risk of cardiovascular diseases and accelerated atherosclerosis [1,2]. Early stages of atherosclerosis are characterized by accumulation of lipids, mainly cholesterol, in arterial macrophages and the formation of macrophage-foam cells [3]. Conversion of macrophages into foam cells involves several mechanisms, including increased cellular lipid peroxidation, increased cellular uptake of lipoproteins and modified lipoproteins, elevated cholesterol biosynthesis rate, and decreased HDL-mediated cholesterol efflux [4]. Cholesterol efflux from macrophages governs reverse cholesterol transport, which is believed to be the main process by which HDL protects against atherosclerosis development [5,6]. Cholesterol efflux from macrophages is mediated by cellular proteins, including the scavenger receptor class B type I (SR-BI), the ATP binding cassette transporter (ABCA1), and the ATP binding cassette transporter gene (ABCG1) [7–10]. ABCA1 stimulates cholesterol efflux to lipid-poor apolipoproteins, while ABCG1 promotes efflux of cholesterol and oxysterols to HDL [6]. SR-BI is a fatty acetylated glycoprotein, which is expressed in hepatocytes and macrophages [11]. The role of SR-BI in HDL interaction with macrophages, however, is still controversial. There is a considerable amount of published evidence that SR-BI is an HDL receptor, which promotes bi-directional flux of cholesterol between cells and HDL [12–14]. On the contrary, several recent studies do not support a major role of SR-BI in cholesterol efflux from macrophage-foam cells [15,16] and in vivo reverse cholesterol transport (RCT) [17].

Cholesterol metabolism was shown in previous reports to be impaired in macrophages isolated from diabetic mice [18,19], including a significant reduction in HDL-mediated cholesterol efflux from the cells. Similar results were also demonstrated in vitro in macrophages incubated with high glucose concentrations [20]. However, the mechanisms involved in these processes are still unknown. The effect of diabetes and of high glucose concentrations on SR-BI or ABCA1 expression remains controversial [21–24]. The goal of the present study is to elucidate whether diabetes influences the expression of proteins involved in cholesterol transport, including ABCA1 and SR-BI.

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Materials and methods

Chemicals

The SR-BI inhibitor BLT1 (block lipid transport-1) was obtained from ChemBridge Corporation (San Diego, CA); BLT-1 was dissolved in DMSO at a concentration of 10 mM, and added to the cells in medium containing 4% BSA at a final concentration of 10 μM. PBS, DMEM, RPMI-1640 medium, FCS (heat-inactivated at 56 °C for 30 min), BSA, penicillin, streptomycin, nystatin, L-glutamine, and sodium pyruvate were from Biological Industries (Beth Haemek, Israel). Fluorescein isothiocyanate (FITC, Sigma–Aldrich); The following antibodies were used: Rat anti mouse ABCA1 (Serotec, Oxford, UK); Rabbit polyclonal anti- SR-BI (Novus Biologicals, NB400-104) was used for FACS; Rabbit polyclonal anti-SR-BI (whole serum, Novus Biologicals, NB400-113) was used for blocking the binding of HDL to SR-BI, and normal rabbit serum (Jackson Immunoresearch Laboratories, Inc. USA) was used as control; Monoclonal anti-β-actin antibody (Sigma).

Mice

C57 Bl/6 mice were randomly divided into 2 groups:

Diabetic mice. The mice were injected intraperitoneally with streptozotocin (200 mg/kg) within 5 min of preparation. Serum glucose levels were determined within 1 week after STZ injection, using a glucometer (Accu-Check Sensor, Roche Manheim, Germany) and mice with serum glucose levels in the range of 250–400 mg/dl were included in the study group. Mice were sacrificed after 3 months. Mice injected with PBS served as control non-diabetic mice.

Cells

Mouse peritoneal macrophages (MPM) isolation. MPM were harvested from the peritoneal fluid of control and diabetic mice, 4 days after intraperitoneal injection of 3 ml of thioglycolate (40 g/L saline) into each mouse. The harvested cells ($10–20 \times 10^6$/mouse) were washed and re-suspended in DMEM containing 5% fetal calf serum (heat-inactivated at 56 °C for 30 min), 100,000 U/L penicillin, 100 mg/L streptomycin, and 2 mmol/L of glutamine. The cell suspension was plated and incubated in a humidified incubator (5% CO_2, 95% air) for adhesion. After 2 h the dishes were washed (2×) in DMEM to remove non-adherent cells. The attached cells were then immediately analyzed for various macrophage functions. Cell viability by trypan blue exclusion was >90%.

J-774 A.1 murine macrophage-like cell line was purchased from the American Type Culture Collection (ATCC, Rockville, MD). J-774A.1 cells were plated at 5×10^5 cells/well in 12-well dish in Dulbecco's modified Eagle's medium (DMEM) supplemented with 5% fetal calf serum (FCS), 100 U penicillin/ml, 100 μg streptomycin/mL, and 2 mM glutamine. The cells were fed every 3 days and used for experiments within 7 days of plating. For in vitro experiments, J-774A.1 macrophages were grown in media containing low vs. high D-glucose concentrations (5–30 mM), or in media containing 5 mM D-glucose and 25 mM L-glucose, for 18 h prior to the experiments. Incubation with 5 mM glucose, which is a normal amount of glucose in the growth medium, served as control non-diabetic condition, whereas incubation of the cells with 30 mM of glucose mimics diabetic situation in mice.

Reverse transcriptase quantitative polymerase chain reaction (Q-PCR) for SR-BI and RT-PCR for ABCA1

Total RNA was extracted with Epicentre commercial kit (Tamar, Israel). cDNA was generated from 1 μg of total RNA using reverse transcriptase (RT) (Boehringer-Mannheim, Germany) and oligo (dT) primers (Boehringer-Mannheim, Germany). The RT reaction was carried out at 37 °C for 50 min and at 70 °C for 15 min.

For SR-BI products of the RT were subjected to Quantitative PCR using TaqMan Gene Expression Assays. Primers and probes for SR-BI and GADPH were designed by TIB Molbiol (Germany). Quantitative PCR was performed on the Rotor-Gene 6000 system (Corbett Life science, Australia). To normalize the data obtained for SR-BI expression, the amount of GADPH mRNA was measured by quantitative PCR as internal standard in all treatments.

For ABCA1 the RT products were subjected to PCR amplification. DNA sequences of upstream (UP) and downstream (DP) primers:

Forward - 5′-GGTTTGGAGATGGTTATACAATAGTTGT-3′;

Reverse - 5′-CCC GGAAACGCAAGTCC-3′;

GADPH cDNA product was used as a standard to equivalent levels of total RNA subjected to RT-PCR.

Macrophage SR-BI protein expression

Flow cytometry (FACS). MPM were washed with ice-cold PBS (2×) and incubated with rabbit anti-SR-BI (1:100), followed by a secondary incubation with donkey-anti-rabbit antibody (Jackson Immuno Research, 1:100) conjugated to Cγ-2. Measurement of cellular fluorescence was determined by FACS at 510–540 nm after excitation of the cells at 488 nm with an argon ion laser. Ten thousand events were registered for each experiment. Cellular fluorescence was quantitated by mean fluorescence intensity (MFI).

Immunocytochemistry. J-774A.1 macrophages were grown on 1.5 mm cover-slides, in Dulbecco's modified Eagle's medium (DMEM) supplemented with 0.2% BSA, 100 U penicillin/mL, 100 μg streptomycin/mL, and 2 mM glutamine overnight. Then, the macrophages were washed with PBS (2×), and fixed with ice-cold acetone during 10 min on ice. Following blocking (T-TBS containing 5% BSA) of non-specific binding sites, cover-slides were stained directly with rabbit anti-SR-BI diluted in blocking solution 1:100, followed by a second incubation with donkey-anti-rabbit antibody (Jackson Immuno Research, 1:100) conjugated to Cγ-2. Propidium iodide was used for counterstaining the macrophage nuclei. Negative controls consisted of slides in which only the second antibody was added. Slides were examined using radiance 2100-confocal imaging system (Bio-Rad), and visualized by a Green HeNe (543 nm) laser and red laser diode (637 nm) (Nikon E600 microscope is an upright Microscope with Plan Apo 60×/1.4 oil Dic objective).

HDL preparation

HDL was isolated from plasma of healthy subjects obtained from the blood bank by continuous density gradient ultracentrifugation [25]. The HDL was then dialyzed against 150 mM NaCl and 1 mM $CaCl_2$ (pH 7.4), and protein content was determined with the Folin phenol reagent [26].

HDL labeling and binding to macrophages

HDL was conjugated with FITC as previously described [27]. HDL (2 mg protein/mL) was dialyzed overnight at 4 °C against several changes of borate buffer containing 0.1 M borate, 25 mM sodium tetraborate, 75 mM NaCl, pH 8.6. Prior to conjugation (1 h), the pH of the dialysis buffer was altered to 9.4. Fluorescein isothiocyanate (FITC) was dissolved in dimethyl formamide and added drop-wise to the HDL to give a final concentration of 0.2 mg/mL and then incubated for 1 h at room temperature with stirring. FITC-conjugated HDL was separated from unconjugated FITC by size exclusion chromatography over a PD-10 column (Amersham-Pharmacia Biotech), eluting with 10 mM phosphate buffer, pH 8.0. Macrophages were incubated at 37 °C for 1 h with FITC-conjugated HDL at a concentration of 10 mg protein/L. Cell association of the lipoproteins was

determined by FACS at 510–540 nm after excitation of the cells at 488 nm with an argon ion laser. Ten thousand events were registered for each experiment. Cellular fluorescence was quantitated by mean fluorescence intensity (MFI).

Alternatively, HDL was radiolabeled with cholesteryl-[C^{14}]-oleate (Amersham, UK) as previously described [28]. Radio-iodinated HDL, at a concentration of 10 μg of protein/L was incubated with the cells at 37 °C for 5 h. Then the cells were washed three times with cold PBS and dissolved in 0.1 mol/L of NaOH. Samples were taken to measure radioactivity and protein.

HDL internalization

J-774A.1 cells were incubated with FITC-HDL at 37 °C for 60 min. Uptake of FITC-HDL was acquired in flow on a multispectral imaging flow cytometer (ImageStream, Amnis Corp., Seattle, WA). Conformation of internalization was assessed of FITC-HDL positive cells, 10,000 single and focused, and FITC-HDL positive cells were collected per sample. Data was analyzed using IDEASTM 3.0.245 Software (Amnis Corp., Seattle, WA).

Cellular cholesterol efflux

J-774A.1 cells were incubated with [3H]-labeled cholesterol for 18 h at 37 °C followed by cell wash in ice-cold PBS (3×) and further incubation in the absence or presence of 100 μg of HDL protein/ml for 3 h at 37 °C. Cellular and medium [^{3}H]-radioactivity was quantitated by β-counter, and HDL-mediated cholesterol efflux was calculated as the ratio of [^{3}H]-label in the medium/[^{3}H]-label in the medium+[^{3}H]-label in the cell.

Macrophage cholesterol mass

Cellular lipids were extracted with hexane:isopropanol (3:2, v:v), and the hexane phase was evaporated under nitrogen. The amount of cellular cholesterol was determined using a kit (CHOL, Roche Diagnostics GMbH, Mannheim, Germany). The remaining cells were dissolved in 0.1 M NaOH for measurement of cellular protein.

Statistical analyses

Each separate experiment was performed in triplicate, and each individual experiment was replicated 3 times ($n = 3$). Statistical analyses used Student's t test for comparing differences between the 2 groups, and one-way ANOVA followed by the Student–Newman–Keuls test was used for comparing differences between multiple groups.

Results

Diabetes was induced in C57Bl/6 mice using streptozotocin (STZ) injection. STZ injection increased serum glucose concentration by 3.5-fold (116 ± 2.3 mg/dl in control mice and 387 ± 1.5 mg/dl in diabetic mice). The expression of ABCA1 protein (Fig. 1A) and mRNA (Fig. 1B) were similar in MPM derived from control or diabetic mice. On the contrary, the expression of SR-BI protein (Fig. 1C) and mRNA (Fig. 1D) were significantly ($p < 0.01$) increased by 1.8 and by more than 3-fold, respectively, in MPM harvested from diabetic mice, compared to MPM harvested from control mice.

Next, we questioned whether the increase in SR-BI expression observed in diabetic MPM could be related to a direct effect of glucose on the cells. For this purpose J-774 A.1 macrophage-like cell line were incubated in vitro with increasing concentrations of glucose (5–30 mM). Similarly to the results obtained ex-vivo, high glucose addition had no effect on ABCA1 protein expression in J-774A.1 macrophages (Fig. 2A), whereas SR-BI protein expression measured by immunocytochemistry (Fig. 2B), was significantly increased, by up to 2-fold in the presence of high glucose levels. The

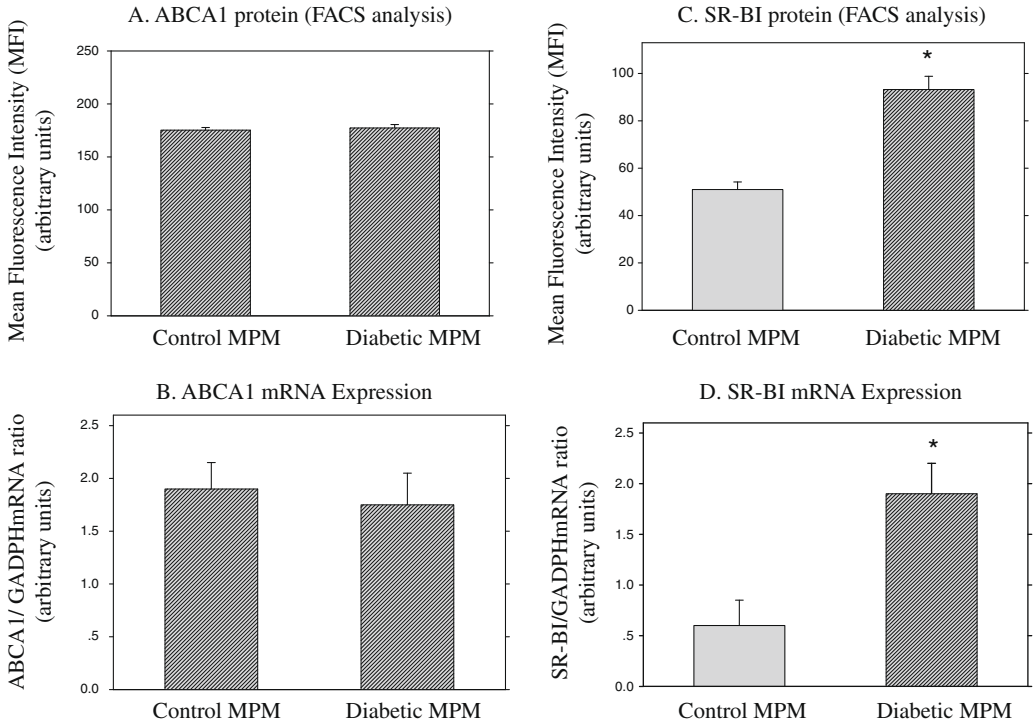

Fig. 1. The effect of diabetes on ABCA1 and SR-BI expression. MPM were harvested from control (Control MPM) or diabetic (Diabetic MPM) mice as described in Materials and methods. ABCA1 (A) and SR-BI (C) protein expression was analyzed by FACS. ABCA1 (B) and SR-BI (D) mRNA expression was determined by RT-PCR and quantitative PCR, respectively. Results represent means ± SD ($n = 3$). *$p < 0.01$ Diabetic MPM vs. Control MPM.

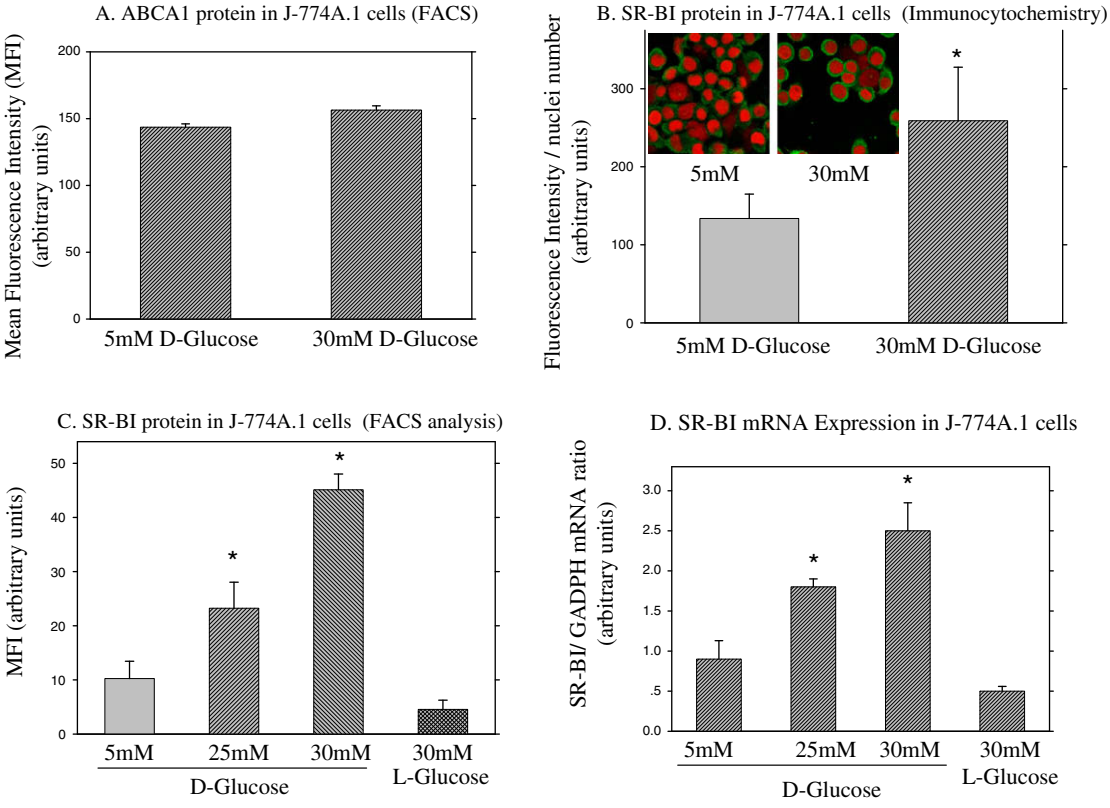

Fig. 2. The effect of glucose on ABCA1 and SR-BI protein expression. J-774 A.1 macrophages were incubated with low (5 mM) or with high (30 mM) glucose concentrations. ABCA1 (A) and SR-BI (B) protein expression were analyzed by FACS, or by immunocytochemistry using Confocal Bio-Rad system. Quantitation of SR-BI protein expression was done by ImagePro program. The inset in (B) shows a representative image. J-774 A.1 macrophages were incubated with increasing concentrations of D-glucose (5, 25, and 30 mM), or with a combination of 5 mM D-glucose and 25 mM L-glucose. SR-BI protein expression was analyzed by FACS (C), and SR-BI mRNA expression was measured by quantitative PCR (D). Results are expressed as the means ± SD of three separate experiments. $^{*}p < 0.01$ vs. 5 mM glucose.

increase in SR-BI protein (Fig. 2C) and mRNA (Fig. 2D) expression was glucose concentration-dependent, and could not be reproduced when the cells were incubated with L-glucose, which does not enter the cells. Accordingly, association of HDL to MPM from diabetic mice was significantly higher compared to MPM from control mice (Fig. 3A). Fig. 3B confirm that high glucose increase the association of radiolabeled-HDL to macrophages (by 28%), and this effect could be related to the increase of SR-BI, as incubation of the cells with HDL in the presence of a rabbit polyclonal anti-SR-BI, which blocks ligand binding to SR-BI, abolished this effect. Moreover, by using the multispectral imaging flow cytometer (ImageStream) system we could demonstrate that high glucose increase the internalization of HDL by the cells by 35%. Addition of the blocking anti-SR-BI reduced HDL internalization by control cells grown with low glucose by 28%, whereas in cells incubated with high glucose blocking of SR-BI decreased HDL internalization by 34%. Altogether these results suggest that the increase in macrophage HDL binding and internalization is related to the increase in SR-BI expression induced by high glucose.

SR-BI was suggested to mediate cholesterol efflux from macrophages. Thus, next we examined the hypothesis that increased macrophage SR-BI expression under diabetic conditions will increase HDL-mediated cholesterol efflux from the cells. Unexpectedly however, HDL-mediated cellular cholesterol efflux from J-774A.1 macrophages that were incubated with high glucose concentrations (30 mM) was significantly decreased, by as much as 34%, in comparison to HDL-mediated cellular cholesterol efflux from cells incubated with low glucose concentration. L-glucose had no effect (Fig. 4A). In parallel, in the presence of high glucose concentrations HDL induced a significant increase in total macrophage cholesterol levels (by 25%) (Fig. 4B). This effect was abolished by blocking anti-SR-BI, or alternatively by using BLT1, a specific inhibitor of lipid transport via the SR-BI, suggesting thus that high glucose induced-HDL interaction with SR-BI results in HDL-cholesterol influx and not efflux.

Discussion

The present study demonstrates, for the first time, that macrophage SR-BI expression increases under diabetic conditions. These results were demonstrated in vivo in diabetic mice, as well as in vitro in macrophages that were grown in the presence of high glucose concentrations. Functionally, the increased SR-BI expression resulted in enhanced binding of HDL to the cells. However, this effect was associated with an unexpected significant reduction in HDL-mediated cholesterol efflux from the cells and an increase in total cellular cholesterol content. Apparently, these results are in contradiction to previous studies showing that the rate of HDL-mediated cholesterol efflux correlates with levels of cellular SR-BI expression [12]. However more recent studies attribute a dual role of SR-BI in cholesterol transport [29,30], as it has been described that it can bind and internalize modified lipoproteins [31] and also mediate the efflux of free cholesterol to HDLs [12]. Thus, macrophage SR-BI can possibly mediate cellular cholesterol removal under physiological conditions, whereas under diabetic conditions SR-BI may induce a selective uptake of HDL-cholesterol ester into the macrophage, leading to foam cell formation. SR-BI contribution to cholesterol export (or import) from macrophages may depend on cellular cholesterol status [32,33] and on the cholesterol gradient between the cell and the

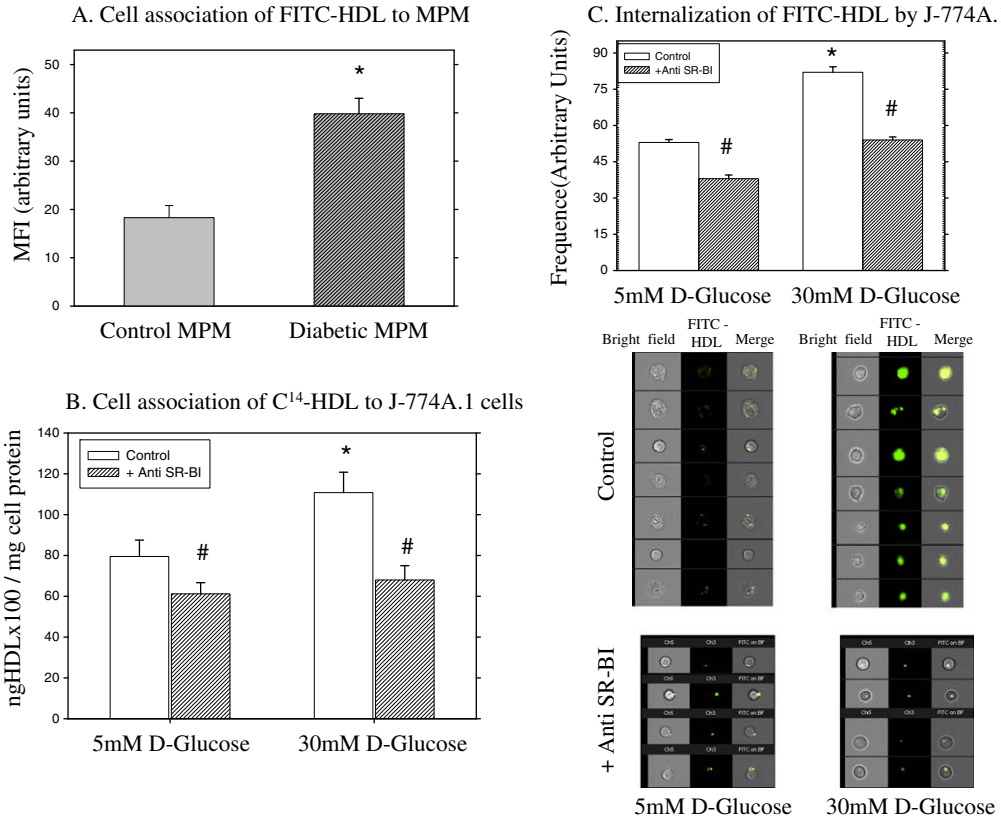

Fig. 3. The effect of diabetes and high glucose on HDL cell association and internalization. MPM from diabetic and control mice were incubated for 1 h with FITC-conjugated HDL at 37 °C. HDL cell-association was measured by FACS (A). J-774A.1 cells were incubated for 5 h at 37 °C with cholesteryl-[C^{14}]-oleate-HDL or with FITC-conjugated HDL in absence or presence of rabbit polyclonal anti-SR-BI. HDL cell-association was measured by counting the radioactivity in the cell lysate (B), and internalization of FITC-HDL was acquired in flow on a multispectral imaging flow cytometer as described in Materials and methods (C). Results are expressed as the means ± SD of three separate experiments. $^{*}p < 0.01$ Diabetic vs. Control, or high (30 mM) vs. low (5 mM) glucose. $^{\#}p < 0.01$ in presence vs. absence of anti-SR-BI.

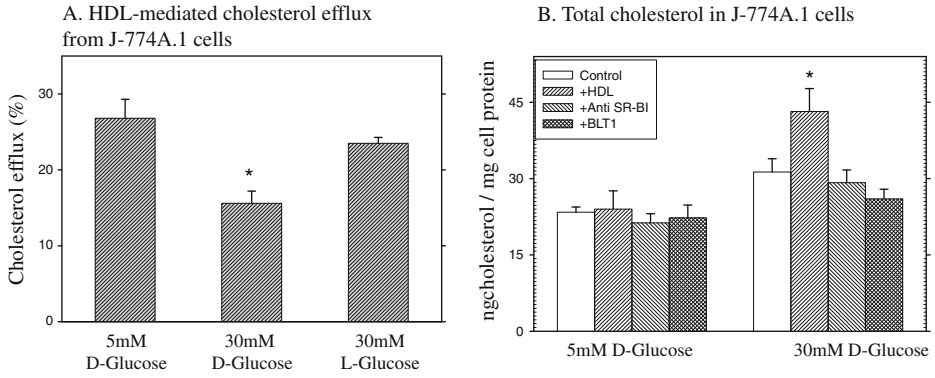

Fig. 4. The effect of glucose on HDL-mediated cholesterol efflux and cholesterol levels in macrophages. (A) J-774 A.1 macrophages were incubated with 5 mM or 30 mM D-glucose or with a combination of 5 mM D-glucose and 25 mM L-glucose. Then, the cells were incubated with [^{3}H]-labeled cholesterol for 18 h at 37 °C and further incubated in the absence or presence of 100 μg of HDL protein/ml for 3 h at 37 °C. HDL-mediated cholesterol efflux was determined in the collected medium. Results are expressed as means ± SD ($n = 3$), $^{*}p < 0.01$ vs. 5 mM D-glucose. (B) J-774 A.1 macrophages were incubated with 5 mM or 30 mM D-glucose in the presence or absence of rabbit polyclonal anti-SR-BI or BLT1 (10 μM). Cellular cholesterol levels were determined in the cellular lipid extracts. Results are expressed as means ± SD ($n = 3$), $^{*}p < 0.01$ with HDL vs. no HDL.

cholesterol acceptor. As high glucose impairs such macrophage cholesterol gradient, it can contribute to the reverse traffic of cholesterol, i.e. from HDL into the macrophages, as indeed was shown in the current study.

Glucose-mediated increase in macrophage SR-BI required glucose uptake by the cells, as only D-glucose (which is taken up by the cells), but not L-glucose (which does not penetrate the cell membrane) exhibited the above effects. These findings are in agreement with our previous studies [19], which demonstrated that only D-glucose induced oxidative stress in macrophages.

The increase in cellular cholesterol levels, which was induced by HDL in the presence of high glucose levels, was abolished by anti-SR-BI and by BLT1, suggesting that these effects depend on SR-BI expression. This is in accordance with previous reports showing that BLT1 specifically inhibits the selective transfer of lipids mediated by SR-BI [34]. The interpretation of this data is that

SR-BI was probably functioning in cholesterol uptake from HDL rather than modulating efflux. Alternatively, it could be promoting HDL uptake, leading to increased cholesterol content. Indeed, by using a new technique of multispectral imaging flow cytometer we could demonstrate an increased HDL internalization by cells incubated with high glucose. Accordingly, Pagler et al. [35] demonstrated that SR-BI mediates endocytosis of HDL, which is followed by HDL resecretion. It is possible that high glucose interferes with the process of HDL resecretion, leading thus to accumulation of HDL-derived cholesterol within the cells.

In summary, our study demonstrates that diabetes stimulates the expression of SR-BI in macrophages and leads to a shift in its activity from HDL-mediated cholesterol efflux to HDL-mediated cholesterol influx. These effects may lead to increased foam cell formation and atherosclerosis development.

Acknowledgments

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