The scavenger receptor-BI (SR-BI) delivers sterols from circulating lipoproteins to tissues, but the relative potency of individual lipoproteins and the transported cholesterol has not been studied in detail. In this study, we used Chinese hamster ovary cells that express recombinant mouse SR-BI but have no functional low density lipoprotein (LDL) receptors (IdlA7-SRBI cells) to compare the fate of lipids transferred from high or low density lipoproteins to cells by SR-BI. HDL and LDL were equally effective in mediating the transfer of \(^{[3]H}\)cholesterol to cells. Only 5% of the free cholesterol transferred to cells was esterified, in direct contrast to the findings in the cells that express LDL receptors in which 50% of the transported cholesterol was esterified. Almost all the free cholesterol transferred from lipoproteins to cells was rapidly excreted when the IdlA7-SRBI cells were switched to media containing unlabelled lipoproteins. SR-BI expression was associated with an increase in selective cholesteryl ester uptake from both lipoproteins, but HDL was a more effective donor. HDL and LDL were equally effective in delivering cholesterol to the intracellular regulatory pool via SR-BI. These data indicate that SR-BI is able to exchange cholesterol rapidly between lipoproteins and cell membranes and can mediate the uptake of cholesteryl esters from both classes of lipoproteins.

Scavenger receptor, class B, type I (SR-BI)\(^1\) is a cell surface receptor that mediates the selective uptake of lipids from lipoproteins to cells (1–3). The uptake of lipoprotein-derived cholesteryl esters through this pathway represents a high capacity, hormone-inducible cholesterol delivery system (4–9). Unlike the classical receptor-mediated endocytic pathway (10), the lipoproteins are not internalized or degraded in the process of delivering sterols to cells (4, 6, 9, 11–13).

As is characteristic of other members of the scavenger receptor family, SR-BI binds multiple ligands with high affinity, including high (HDL), low (LDL), and very low density lipoproteins, oxidized LDL, acetylated LDL, and anionic phospholipids (1, 14–17). SR-BI mediates the uptake of cholesteryl esters from HDL (1) and also nonlipoprotein cholesterol by cells (3). SR-BI is equally efficient at mediating the import and export of cholesterol to and from cells to lipoproteins and other acceptors (2, 3).

Previously, we showed that SR-BI expression was associated with an increase in lipoprotein-stimulated cholesterol esterification in cells lacking LDL receptors (3). LDL and HDL were equally effective ligands for the SR-BI-dependent stimulation of cholesterol esterification within cells. Moreover, free cholesterol was a potent stimulus for the formation of cholesteryl esters in cells that express high levels of SR-BI. We did not define the chemical nature of the lipoprotein-associated lipid that was responsible for the SR-BI-dependent stimulation of esterification. In this study we determined the relative contributions of free cholesterol and cholesteryl esters to the formation of intracellular cholesteryl esters and examined the intracellular fate of these different lipids following uptake via SR-BI. We also examined the availability of the free cholesterol transferred to cells by SR-BI for efflux. Finally, the relative potency of HDL and LDL as donors to the intracellular cholesterol regulatory pool was determined.

**EXPERIMENTAL PROCEDURES**

**Cell Lines and Tissue Culture—**Chinese hamster ovary (CHO) cells that lack LDL receptor activity (IdlA7 cells) (18) and express high levels of recombinant SR-BI (IdlA7-SRBI) were used in this study (3). These cells have the advantage of allowing the analysis of the effect of SR-BI expression on lipid transport to cells from LDL that is independent of the LDL receptor. The cells were maintained in medium A (1:1 mixture of Dulbecco’s minimal essential medium and Ham’s F-12 medium with 100 units/ml penicillin, and 100 \(\mu\)g/ml streptomycin sulfate), supplemented with 5% (v/v) fetal calf serum, and 0.25 mg/ml Geneticin\(^\text{TM}\) (G418 sulfate, Life Technologies, Inc., Grand Island, NY). The cells were plated in 6-well plates at a cell density of 60,000 cells/well in medium A with 5% (v/v) fetal calf serum. On day 2, the cells were washed twice with phosphate-buffered saline (PBS) and refed with medium A containing 5% (v/v) newborn calf lipoprotein-deficient serum, 10 \(\mu\)M compactin, and 100 \(\mu\)M mevalonate. On day 3 the cells were washed with PBS and switched to medium B (Dulbecco’s modified Eagle’s medium (minus glutamine) with 2 mg/ml fatty acid-free bovine serum albumin).

**Lipoproteins—**Human HDL (density (d) = 1.09–1.21 g/liter) and LDL (d = 1.04–1.063 g/liter) were prepared as described previously (19). The lipoproteins were iodinated using the iodine monochloride method (20). The HDL and LDL were labeled by Celite exchange with either \(^{125}\)Icholesterol oleoyl ether (Amersharm Pharmacia Biotech), \(^{14}C\)cholesterol oleate (Amersharm Pharmacia Biotech), or \(^{3}H\)cholesterol (NEN Life Science Products Inc.), as described (21).

**Cholesterol Esterification—**On day 3 the cells were incubated in medium B plus varying concentrations of HDL or LDL. After a 5-h incubation with lipoproteins, the cells were pulsed with 0.2 mM \(^{14}C\)oleate (~10,000 dpm/nmol) (NEN Life Science Products Inc., Boston, MA) for 2 h. Then the cells were washed three times with buffer A
LDL and HDL were labeled with \( ^{3} \)H-cholesterol or \( ^{3} \)H-cholesterol and cholesteryl esters into cells via SR-BI, HDL and LDL particles were labeled with \( ^{3} \)H-cholesterol or \( ^{3} \)H-cholesterol ester and incubated with mutant CHO cells that express no functional LDL receptors (IdIA7 cells) (18) and a line of permanently transfected idIA7 cells that express high levels of recombinant mouse SR-BI (IdIA7-SRBI cells) (3). In the first experiment, the \( ^{3} \)H-cholesterol-labeled lipoproteins were incubated with the cells for 5 h in the presence or absence of an inhibitor of acyl-coenzyme A:cholesterol acyltransferase inhibitor (Sandoz compound 58-035). We added unlabeled 0.2 mCi olate to the cells for 2 h prior to extraction of the cellular lipids and analysis by TLC. Panels A–C of Fig. 1 shows the amount of \( ^{3} \)H-cholesterol associated with the IdIA7-SRBI and the control IdIA7 cells after the cells were incubated with the indicated amounts of radiolabeled HDL or LDL. An increase in the cellular content of \( ^{3} \)H-cholesterol was seen with both lipoproteins, but only in the cells that express SR-BI. When the data were plotted on the basis of the protein content of lipoproteins, LDL appeared to be a more effective cholesterol donor than HDL (panel A), but if the data were plotted on the basis of the total cholesterol added, the two lipoproteins were relatively very similar (panel B). The acyl-coenzyme A:cholesterol acyltransferase inhibitor did not significantly change the amount of radiolabeled cholesterol transferred to cells, except for a small reduction at the highest levels of LDL used in the assay. Addition of chlo-roquine also had no effect on the amount of \( ^{3} \)H-cholesterol.

FIG. 1. Uptake of \( ^{3} \)H-cholesterol (panels A–C) and formation of \( ^{3} \)H-cholesterol ester (panels D–F) from LDL and HDL in IdIA7 and IdIA7-SRBI cells. IdIA7 and IdIA7-SRBI cells were seeded in 6-well plates at a cell density of 60,000 cells/well in medium A containing 5% fetal calf serum. On day 2 the cells were washed twice with PBS and incubated with medium A plus 5% newborn calf lipoprotein-deficient serum, 10 \( \mu \)g ml protein, and 100 \( \mu \)g ml mevalonate. On day 3, the cells were washed 3 times with PBS before the addition of medium B plus the indicated amount of \( ^{3} \)H-cholesterol LDL (23,000 cpm/nmol) or HDL (220,000 cpm/nmol) in the absence (duplicate incubation) or presence (single incubation) of a 40-fold excess of unlabeled lipoproteins. An acyl-coenzyme A:cholesterol acyltransferase inhibitor (Sandoz compound 58-035) was added 5 min prior to the lipoproteins. After a 5-h incubation, 0.2 mCi olate was added to the cells for 2 h. Then the cells were washed 3 times with buffer A and once with buffer B. The cells were then dissolved in 1 ml of 0.1N NaOH and the lipid composition was analyzed using TLC as described under “Experimental Procedures.” The cells were lysed in 1 ml of 0.1 N NaOH and the protein was quantitated using the Lowry method (22). The experiment was repeated three times and the results were similar.

RESULTS

To determine the relative abilities of SR-BI to transport cholesterol and cholesteryl esters into cells via SR-BI, HDL and LDL particles were labeled with \( ^{3} \)H-cholesterol or \( ^{3} \)H-cholesterol ester and incubated with mutant CHO cells that express no functional LDL receptors (IdIA7 cells) (18) and a line of permanently transfected IdIA7 cells that express high levels of recombinant mouse SR-BI (IdIA7-SRBI cells) (3). In the first experiment, the \( ^{3} \)H-cholesterol-labeled lipoproteins were incubated with the cells for 5 h in the presence or absence of an inhibitor of acyl-coenzyme A:cholesterol acyltransferase inhibitor (Sandoz compound 58-035). We added unlabeled 0.2 mCi olate to the cells for 2 h prior to extraction of the cellular lipids and analysis by TLC. The cells were then dissolved in 1 ml of 0.1 N NaOH and the protein was quantitated using the Lowry method (22). Silver nitrate-Silica Gel 60 plates were used for the TLC in the re-esterification experiments (23).
transferred to cells (data not shown). From these results, we conclude that the amount of cholesterol transferred from lipoproteins to cells is not dependent on the protein composition of the lipoprotein particle, but rather on the amount of lipoprotein cholesterol provided to the cells, and that inhibition of cholesterol esterification does not affect the cellular uptake of free cholesterol from lipoproteins via SR-BI.

To determine the amount of \(^{3}H\)cholesterol that was ultimately delivered to the ER and esterified, the amount of \(^{3}H\)cholesteryl esters formed during the experiment was measured. A significant, although small, percentage (~5%) of the total \(^{3}H\)cholesterol delivered to cells was converted to \(^{3}H\)cholesteryl esters (Fig. 1, panels D–F) in the cells expressing SR-BI. As expected, no \(^{3}H\)cholesteryl esters were formed in the absence (duplicate incubation) or presence (single incubation) of a 40-fold excess of unlabeled lipoproteins. Cells were harvested after 1, 3, and 5 h. At the end of the 5-h incubation, three sets of cells were washed with PBS and unlabeled lipoproteins were added to the cells. These cells were incubated for an additional 1, 2, or 3 h prior to harvesting. The lipids were analyzed by TLC as described in the legend to Fig. 1. The experiment was repeated 5 times and the results were similar.

To determine if the cholesterol transferred to cells from lipoproteins via SR-BI is accessible for efflux, a time course experiment was performed in which the cells were incubated with lipoproteins labeled with \(^{3}H\)cholesterol for up to 5 h, washed, and then unlabeled lipoproteins were added to the media (Fig. 2). \(^{14}C\)Oleate was present throughout the experiment to follow cholesterol esterification. The amount of \(^{3}H\)cholesterol transferred to the cells expressing SR-BI increased progressively during the initial 5-h incubation, and then decreased with the addition of unlabeled lipoproteins (panel A). The media was subjected to ultracentrifugation and all of the \(^{3}H\)cholesterol was associated with the lipoprotein fraction (data not shown). The LDL used in this experiment had a 4-fold higher cholesterol content than the HDL, which accounts for the greater amount of \(^{3}H\)cholesterol transferred from LDL than HDL to cells during this experiment. Only a modest increase in cellular content of \(^{3}H\)cholesterol was seen in the IdlA7 cells (panel B). Previous studies have shown that these cells express low but detectable levels of SR-BI (3). A modest increase in the cellular content of \(^{3}H\)cholesterol that was not reversible was seen in the CHO cells (panel C), which contain a similar amount of SR-BI as the IdlA7 cells (data not shown) but also express LDL receptors.

We next determined how much of the \(^{3}H\)cholesterol that entered cells in this experiment was converted to \(^{3}H\)cholesteryl esters (Fig. 2, panels D–F). In the IdlA7-SRBI cells, ~5% of the \(^{3}H\)cholesterol from HDL or LDL was esterified at the 5-h time point. A similar mass of cholesteryl esters was formed in the CHO cells, but this represented a much higher proportion of the free cholesterol that entered the cells (~50%). Only a trace amount (<2%) of the HDL-associated \(^{3}H\)cholesterol that entered CHO cells was esterified. The total amount of cholesteryl \(^{14}C\)oleate formed during the experiment was monitored (Fig. 2, panels G–I) and proceeded in an unimpeded fashion in both the IdlA7-SRBI cells and CHO cells (panels G and I, respectively). LDL stimulated a dramatic increase in cholesteryl esterification in CHO cells (panel I), which is consistent with the known re-esterification of LDL cholesterol delivered to the ER via the LDL receptor pathway (10).

SR-BI not only mediates the transfer of free cholesterol between lipoproteins and cells, but also promotes the selective uptake of cholesteryl esters from HDL to cells (1). To determine if LDL is as effective a donor of cholesteryl esters as HDL, we labeled the lipoprotein particles with \(^{3}H\)cholesteryl oleoyl ether (which cannot be hydrolyzed) and incubated the radiolabeled lipoproteins with cells expressing recombinant SR-BI (Fig. 3). A 4-fold greater amount of the \(^{3}H\)cholesteryl oleoyl ether from HDL was associated with the IdlA7-SRBI cells than with the IdlA7 or CHO cells (Fig. 3, panel A), which is similar to what has been previously reported. As expected, when LDL was substituted for HDL in the experiment, the CHO cells had the greatest amount of cell-associated \(^{3}H\)cholesteryl oleoyl ether. SR-BI overexpression was associated with an ~2-fold increase in delivery of cholesteryl ethers from LDL to the cells (Fig. 3B).

To determine if the transfer of cholesteryl esters from LDL to
cells occurs in the absence of lipoprotein degradation, we radiolabeled the protein component of HDL and LDL with radioactive iodine and the cholesteryl esters of the lipoproteins with tritium (Fig. 4). Essentially no protein degradation was seen in the IdlA7 cells treated with HDL or LDL (panels A and B). As expected, a dose-dependent increase in lipoprotein degradation was seen when LDL, but not HDL, was added to the CHO cells.

The cellular lipids were subjected to TLC to determine the fate of the lipoprotein-associated [3H]cholesteryl oleate (Fig. 4, panels C and D). Addition of radiolabeled HDL to the IdlA7-SRBI cells resulted in an increase in the cellular content of [3H]cholesteryl oleate, but no increase was seen in the IdlA7 or CHO cells (panel C). When radiolabeled LDL was used, the increase in cellular [3H]cholesteryl oleate was of similar magnitude in the IdlA7-SRBI cells and CHO cells (panel D).

To determine if the [3H]cholesteryl oleate uptake taken up from the HDL and LDL was hydrolyzed to [3H]cholesterol, we measured the cellular content of [3H]cholesterol (Fig. 4, panels E and F). In the IdlA7-SRBI cells incubated with radiolabeled HDL, more than 65% of the [3H]cholesterol that entered the cell was hydrolyzed to free cholesterol (panel E). A small but measurable increase in the cellular content of [3H]cholesterol was seen in the control IdlA7 cells, whereas almost no change was seen in CHO cells. In the IdlA7-SRBI and CHO cells, more than 70% of the radiolabeled cholesterol that entered the cells from LDL was in the free form. Almost all the [3H]cholesteryl oleate that entered the IdlA7 cells from HDL had undergone hydrolysis and was in the free form (panel F). The high cellular content of [3H]cholesterol in these cells was not due to the presence of an esterase in the lipoprotein particles, since TLC analysis of lipoprotein lipids revealed that greater than 98% of the radioactivity was cholesteryl ester. Thus, SR-BI transports cholesteryl esters from both classes of lipoproteins but is significantly more efficient in delivering core hydrophobic lipids from HDL than from LDL.

To determine how much of the cholesteryl ester that enters cells via SR-BI is hydrolyzed and then re-esterified, the experiments shown in Fig. 4 were repeated using HDL labeled with [3H]cholesteryl linoleate. The amount of [3H]cholesteryl oleate formed was determined by extracting the lipids from the cells and separated using Silica Gel 60 TLC plates impregnated with AgNO3 (23), which allows the separation of cholesteryl linoleate from cholesteryl oleate (Fig. 5). In the IdlA7-SRBI cells, approximately 50% of the [3H]cholesteryl linoleate was hydrolyzed to [3H]cholesterol and only 5% was re-esterified to form cholesteryl oleate (panel C).

To determine if the lipoprotein-associated lipids transported from HDL and LDL into cells via SR-BI have the same regulatory effects, we examined the effect of SR-BI expression on the level of immunodetectable HMG-CoA reductase (Fig. 6A) and the processing of SREBP-2 (Fig. 6B) in response to addition of LDL and HDL with a similar cholesterol content. Two proteins with apparent molecular masses of 97 and 190 kDa were seen in most lanes (Fig. 6A), which represent the monomeric and dimeric forms of HMG-CoA reductase, respectively (29–31). After addition of 10 μg/mL LDL, the level of immunodetectable HMG-CoA reductase did not change in either the IdlA7-SRBI or IdlA7 cells, but fell to very low levels in the CHO cells (Fig. 6A). Addition of higher levels of LDL (100 μg/mL) resulted in a decrease in the level of HMG-CoA reductase in both the IdlA7-SRBI and CHO cells, but not the IdlA7 cells; when an equivalent amount of cholesterol was added as HDL (400 μg/mL), there was a similar decrease in the amount of HMG-CoA reductase in the IdlA7-SRBI cells. Thus, in the absence of LDL receptors and in the presence of very high levels of lipoproteins,
SR-BI can transport sufficient cholesterol from LDL to the cholesterol regulatory compartment to down-regulate cholesterol-responsive genes. Addition of 25-hydroxycholesterol, which freely diffuses through the cell membrane, reduced the levels of HMG-CoA reductase in all cells.

In parallel dishes, the nuclei were isolated from the cells and the extracts were examined for the presence of the mature form of SREBP-2 (Fig. 6B). In cholesterol-loaded cells, SREBP-2 is anchored to the ER membrane in a hairpin configuration (24, 26). Cholesterol depletion results in proteolytic processing of the protein and release of a ~66-kDa, N-terminal fragment into the cytoplasm. This mature form of SREBP-2 then diffuses into the nucleus where it activates multiple cholesterol-regulated genes (26). Immunoblot analysis from the nuclear fractions of the three cell lines revealed a protein with an apparent molecular mass of ~66 kDa, which represents the mature form of SREBP-2. A 56-kDa protein, which is a proteolytic product of the mature form of SREBP-2, was also present. A band of similar size has been previously observed when the nuclei are isolated from cells (26). The pattern of expression of the mature form of SREBP-2 in the IdlA7-SRBI, IdlA7, and CHO cells (Fig. 6B) mirrored that which was seen for HMG-CoA reductase (Fig. 6A).

To determine if the time course of down-regulation of HMG-CoA reductase was similar when sterols were supplied to cells as HDL or LDL, equivalent amounts of cholesterol were provided to cells as a constituent of either lipoprotein (Fig. 7). The level of HMG-CoA reductase began decreasing at 2 h and was almost undetectable at 8 h in the IdlA7-SRBI cells incubated with either LDL (100 μg/ml) or HDL (400 μg/ml) (Fig. 7). Thus, no lipoprotein class-specific differences were seen in the regulatory effects of SR-BI mediated uptake of sterols from HDL and LDL. No change in the level of HMG-CoA reductase was seen in the IdlA7 cells with the addition of lipoproteins, whereas in the CHO cells, the level of immunodetectable HMG-CoA reductase fell when LDL, but not HDL, was added to the media. As expected, treatment with 25-hydroxycholesterol decreased the levels of HMG-CoA reductase in all three cell lines, confirming that the integrity of the cholesterol regulatory machinery remained intact. No change in protein level was seen in the cells incubated without lipoproteins.

**DISCUSSION**

In this paper we examined and compared the effect of the high level SR-BI expression on the transfer and fate of lipids from LDL and HDL to CHO cells. A new observation made in this paper is that SR-BI transferred more free cholesterol than cholesteryl esters to cells from either LDL or HDL. Almost all the lipoprotein-associated cholesterol that entered cells via SR-BI was available for efflux, which suggests that most of the cholesterol transferred to cells remains in the plasma membrane and/or in a freely accessible cholesterol pool. A small, but measurable fraction (~5%) of the free cholesterol transferred to the cells in an SR-BI dependent fashion was delivered to the ER and esterified by acyl-coenzyme A:cholesteryl acyltransferase. We also showed that HDL was a more efficient donor of cholesteryl esters than LDL, although SR-BI was able to mediate the selective uptake of core lipids from both classes of lipoproteins. Over half of the transported cholesteryl esters were converted to free cholesterol, and ~5% of this free cholesterol was re-esterified. Finally, sterols transported from LDL or HDL by SR-BI were equally effective in delivering cholesterol to the intracellular regulatory cholesterol pool, as revealed by...
inhibition of SREBP-2 processing and a reduction in HMG-CoA reductase protein mass.

Previously we demonstrated that uptake of non-lipoprotein-associated cholesterol is enhanced by SR-BI expression (3). The current studies extend these results and show that SR-BI also mediates cellular uptake of free cholesterol from LDL and HDL. In CHO cells, most of the cholesterol remains in the plasma membrane and is readily available for efflux via SR-BI. Only a fraction of the free cholesterol that enters cells in a SR-BI-dependent manner is transported to the ER where it is available for esterification. The situation would be different in steroidogenic cells since most of the cholesterol transported into these cell types would be routed into the steroidogenic pathway. It has been shown that HDL cholesterol provides a greater proportion of the substrate for steroidogenesis in rat luteal cells than does LDL cholesteryl esters (32, 33). In the liver, it is likely that SR-BI is involved in the transport of free cholesterol from circulating lipoproteins into hepatocytes, and then into the bile (34). In liver perfusion studies of African green monkeys, HDL cholesterol is more efficiently transported into bile than are LDL cholesteryl esters (35). Unlike what we have observed in cultured cells, the cholesterol transferred from HDL to the bile may not enter the intra-hepatocyte regulatory pool but be transferred directly to the biliary system via the plasma membrane (36).

We and others have shown that SR-BI can mediate both the influx and efflux of cholesterol from cells to lipoproteins and other acceptors (2, 3, 37). Here we show that almost all of the free cholesterol delivered to cells via SR-BI is readily available for efflux, indicating that there is a constant bidirectional exchange of free cholesterol between cells and lipoproteins that is facilitated by SR-BI (Fig. 2). The direction of cholesterol flux between cells and lipoproteins is not concentration-dependent, since the concentration of lipoproteins was never changed during the experiment. Morrison et al. (38) showed that the rate of uptake of emulsion-associ ated unesterified cholesterol in a system free of membrane proteins or apolipoproteins is independent of acceptor concentration and so exhibits first-order kinetics, which is consistent with the results of our studies.

Inhibition of esterification had no measurable effect on the amount of cholesterol transported from lipoproteins to cells (Fig. 1). Therefore, the transport of cholesterol at the cell surface does not reflect changes in the cholesterol content of the ER. The cholesterol exchange that is mediated by SR-BI is not affected by the inhibition of lysosomal transport by chloroquine. These data are consistent with previous findings that lysosomotropic agents do not affect the utilization of HDL-associated free or esterified cholesterol for steroidogenesis (33).

SR-BI expression was associated with the selective transport of cholesteryl esters from LDL as well as HDL. The LDL used in these studies did not contain any immunodetectable apoA-I (data not shown), which indicates that apoA-I is not required for efficient SR-BI-mediated transfer of cholesterol to cells. The finding that SR-BI can mediate the selective uptake of cholesteryl esters from LDL is consistent with the observations of Reaven et al. (9) who showed that 20% of the LDL cholesteryl ether delivered to cAMP-stimulated granulosa cells is taken up by a selective mechanism and that the stimulation of rat granulosa cells with cAMP resulted in a proportionally greater increase in the selective uptake of cholesteryl esters than whole lipoprotein particle uptake of LDL (8).

An unexpected finding was the relatively large amount of [3H]cholesteryl oleoyl ether associated with the ldlA7 cells when it was provided as a constituent of LDL but not HDL (Fig. 3). Similar results were obtained when cells were incubated with LDL in which the cholesteryl esters were labeled (see Fig. 4). The LDL cholesteryl ether particles did not nonspecifically adsorb to the surface of the ldlA7 cells since only very low levels of cell-associated radioactivity were seen when ldlA7 cells were incubated with [3H]-LDL particles under identical conditions (data not shown). Multiple methodologies were used to label the LDL (Celite exchange, dimethyl sulfoxide-assisted labeling or particle reconstitution) and identical results were obtained (data not shown). It is possible that another nonspecific pathway is operative that accounts for the observed association of LDL-derived cholesteryl esters in these cells.

Cholesteryl esters were more efficiently transferred from HDL to cells than from LDL. The greater efficiency of HDL may be explained by the smaller size of the HDL particles and the resultant lower diffusion barrier (38). These physical characteristics serve to increase the probability that the HDL particle will have intimate contact with the cell membrane during collision events. It is also possible that other factors, such as the composition and packing of the phospholipid molecules on the HDL surface, may influence lipid transfer.

Here we show that cholesterol delivered to cells via SR-BI has important regulatory effects on genes and proteins involved in cholesterol metabolism. Cholesterol delivered to cells via SR-BI from both HDL and LDL down-regulated HMG-CoA reductase and inhibited SREBP-2 processing. The in vivo role of SR-BI in the transport of lipids from apoB- and apoE-containing lipoproteins is less clear than that for HDL since most
cells in the body express LDL receptors, which is the major pathway by which these lipoproteins are removed from the plasma. Fielding et al. (39) have shown that free cholesterol is selectively transferred from LDL to fibroblasts that have been cultured in media containing human plasma, which down-regulates the LDL receptor pathway (39, 40). SR-BI may contribute to the LDL receptor-independent pathway of LDL cholesterol uptake by some tissues.

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