Phospholipid Transfer Protein Interacts with and Stabilizes ATP-binding Cassette Transporter A1 and Enhances Cholesterol Efflux from Cells*

Phospholipid transfer protein (PLTP) is ubiquitously expressed in animal tissues and plays multiple roles in lipoprotein metabolism, but the function of peripheral PLTP is still poorly understood. Here we show that one of its possible functions is to transport cholesterol and phospholipids from cells to lipoprotein particles by a process involving PLTP interactions with cellular ATP-binding cassette transporter A1 (ABCA1). When ABCA1 was induced in murine macrophages or ABCA1-transfected baby hamster kidney cells, PLTP gained the ability to promote cholesterol and phospholipid efflux from cells. Although PLTP alone had lipid efflux activity, its maximum activity was observed in the presence of high density lipoprotein particles. Pulse-chase studies showed that the interaction of PLTP with ABCA1-expressing cells played a role in promoting lipid efflux. Overexpression of ABCA1 dramatically increased binding of both PLTP and apoA-I to common sites on the cell surface. Both PLTP and apoA-I were covalently cross-linked to ABCA1, each protein blocked cross-linking of the other, and both PLTP and apoA-I stabilized ABCA1 protein. These results are consistent with PLTP and apoA-I binding to ABCA1 at the same or closely related sites. Thus, PLTP mimics apolipoproteins in removing cellular lipids by the ABCA1 pathway, except that PLTP acts more as an intermediary in the transfer of cellular lipids to lipoprotein particles.

Phospholipid transfer protein (PLTP) plays important and diverse roles in lipoprotein metabolism (1, 2). Plasma PLTP transfers phospholipids between lipoproteins and remolds high density lipoprotein (HDL) to generate lipid-poor particles (3–7), and hepatic PLTP facilitates the production of triglyceride-rich apoB-containing particles in mice (8, 9). PLTP is expressed ubiquitously in human and mouse tissues (5, 10, 11), suggesting that it may locally modulate lipid metabolism in peripheral tissues. Little is known, however, about the interactions of PLTP with peripheral cells and its effects on cellular lipid metabolism.

One possible function of peripheral PLTP is to transport lipids from cells to lipoproteins. Cholesterol efflux from cells occurs by at least two distinct mechanisms mediated by different components in HDLs (12, 13). HDL phospholipids sequester cholesterol that desorbs from the plasma membrane, and lipid-poor HDL apolipoproteins remove both cholesterol and phospholipids by an active transport process. A cell surface receptor called scavenger receptor B1 facilitates cholesterol transport from cells to HDL phospholipids (13), whereas a sterol-inducible membrane transporter called ATP-binding cassette transporter A1 (ABCA1) mediates the removal of cholesterol and phospholipids by lipid-poor apolipoproteins (14). It is possible that PLTP enhances one or both of these lipid efflux pathways in peripheral tissues.

We reported previously that PLTP enhanced cholesterol and phospholipid efflux from cholesterol-loaded human fibroblasts in the presence of HDL particles (15). In contrast, PLTP had no effect on lipid efflux from fibroblasts isolated from a patient with Tangier disease, an HDL deficiency syndrome discovered later to be caused by mutations in ABCA1 (16–19). These findings suggested that PLTP enhanced lipid efflux only by ABCA1-dependent mechanisms. The discovery of ABCA1 has allowed us to address in more detail the role of ABCA1 in this PLTP-enhanced lipid efflux. Our current findings confirm that ABCA1 expression is required for PLTP lipid efflux activity and that this probably involves direct interactions of PLTP with ABCA1. These studies suggest a model whereby PLTP mimics apolipoproteins in removing cellular lipids by the ABCA1 pathway, except that PLTP requires the presence of lipoprotein acceptor particles for optimum lipid transport activity.

EXPERIMENTAL PROCEDURES

Lipoproteins, ApoA-I, and Phospholipid Vesicles—LDL and HDL were prepared by sequential ultracentrifugation in the density range 1.019–1.063 and 1.125–1.21 g/ml, respectively, and HDL was depleted of apoE and apoB by heparin-agarose chromatography (20). Trypsinized HDL was prepared as previously described (21) by treating HDL with trypsin for 30 min at 37 °C at an HDL/trypsin protein ratio of 40:1. This procedure digests ~20% of the total HDL protein content of HDL without disturbing its lipid composition. ApoA-I was purified from HDL, delipidated, and labeled with 125I as described previously (20). LDL was acetylated by the method of Goldstein et al. (22). Phospholipid vesicles were prepared with phosphatidylcholine by sonication as described (23).

Recombinant PLTP—Recombinant wild-type and mutant PLTP was isolated by Ni²⁺-nitrilotriacetic acid resin column chromatography from serum-free conditioned culture medium collected from baby hamster kidney (BHK) cells transfected with a His-tagged human PLTP cDNA using methotrexate as selection agent (5). The isolated PLTP fractions were assayed for phospholipid transfer activity and for purity by SDS-PAGE. Mutant PLTP contained four amino acid substitutions (L16R,
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L69P, Q270R, and S387P) as described previously (24). PLTP was labeled with 125I using the IODO-BEAD iodination reagent (Pierce) and Na125I to a specific activity of 400–500 cpm/μg of protein, and the integrity of the 125I-PLTP was verified by autoradiography of SDS-PAGE gels.

Cell Culture and Lipid Efflux—Murine J774 macrophages and BHK cells were obtained from the ATCC (Manassas, VA). BHK cells expressing human ABCA1 were generated using the mifepristone-inducible GeneSwitch System (Invitrogen) as described (25). Control (mock) BHK cells were derived from the same clonal line transfected with plasmids lacking the ABCA1 cDNA insert. All cells were grown and maintained in DMEM containing 10% fetal bovine serum until experimental treatments. To induce ABCA1 expression, J774 macrophages were incubated for 24 h with DMEM containing 1 mg/ml bovine serum albumin (DMEM/BSA) plus 50 μg/ml acetylated LDL followed by 20–24-h incubations with DMEM/BSA plus 0.5 mM 8-Br-cAMP (26), and ABCA1-transfected BHK cells were incubated for 24 h in DMEM/BSA plus 10 nm mifepristone (25). Control macrophages were treated identically except without 8-Br-cAMP, and control BHK cells were mock transfectants treated identically.

To radiolabel cellular cholesterol, 0.5–1 μCi/ml [3H]cholesterol (PerkinElmer Life Sciences) was added to the acetylated LDL medium (macrophages) or to the growth medium 24 h prior to mifepristone treatment (BHK cells) (26). To label phospholipids, 1 μCi/ml [methyl-3H]choline chloride (PerkinElmer Life Sciences) was added to the incubation medium followed by two washes of cells (27).

To measure lipid efflux, cells were incubated with DMEM/BSA with or without the indicated acceptor particles for 2–6 h at 37 °C and chilled on ice, and the medium was collected and centrifuged to remove detached cells. For cholesterol efflux, the medium was counted for 3H, and the cells were assayed for free and esterified [3H]cholesterol after isolation by thin layer chromatography (27). For phospholipid efflux, medium and cellular choline-labeled phospholipids were extracted in chloroform/methanol and assayed for 3H radioactivity (27). Lipid efflux was calculated as the percentage of free [3H]cholesterol or [3H]choline-labeled phospholipid released from the medium.

Cell Surface and ABCA1 Binding of ApoA-I and PLTP—For the competitive sequential binding assay, BHK cells were first incubated for 4 h at 37 °C with DMEM/BSA containing the indicated concentrations of either apoA-I or PLTP, chilled to 0 °C, washed twice with ice-cold PBS/BSA, and then incubated for 2 h with ice-cold HEPES-buffered DMEM/BSA containing 2 μg/ml 125I-apoA-I or 125I-PLTP with or without 300 μg/ml unlabeled apoA-I or PLTP, respectively. Cells were washed twice at 0 °C with PBS/BSA and twice with PBS, and cell-associated radioactivity and cell protein were measured after digestion with 0.1 N NaOH (26). Results are expressed as ng of 125I-apoA-I or 125I-PLTP per mg of cell protein after subtraction of values in the presence of unlabeled apoA-I or PLTP, respectively.

For the ABCA1 binding assay, BHK cells were incubated for 2 h at 37 °C with 2 μg/ml 125I-PLTP or 125I-apoA-I without or with a 200 μg/ml concentration of either PLTP or apoA-I, washed twice with ice-cold PBS, incubated for 30 min at 0 °C with PBS containing 1 mg/ml DSS (cross-linking agent), washed twice with cold PBS containing 20 mM glycine (to quench cross-linker), and extracted with detergent. ABCA1 was isolated by immunoprecipitation and SDS-PAGE, and 125I-labeled ABCA1 was detected by PhosphorImaging (26).

Metabolic Labeling of ABCA1—Cells were incubated for 15 min at 37 °C with DMEM/BSA containing 100 μCi/ml [35S]methionine (Amer sham Biosciences). Cells were washed and dislodged from the dish at 0 °C in buffer containing protease inhibitors. ABCA1 was isolated by immunoprecipitation and SDS-PAGE, and 35S-labeled ABCA1 was detected by PhosphorImaging.

ABCA1 Stabilization—Cholesterol-loaded J774 macrophages were incubated with DMEM/BSA plus 0.5 mM 8-Br-cAMP for 20 h, washed twice with PBS/BSA, and then incubated for 6 h with DMEM/BSA with or without 8-Br-cAMP with or without either 10 μg/ml apoA-I or PLTP. Microsomal membranes were isolated from homogenized cells by ultracentrifugation, membrane proteins were solubilized in SDS buffer and resolved by SDS-PAGE, and ABCA1 was identified by immunoblot analysis (26). Equal amounts of membrane protein were added per gel lane.

RESULTS

Our previous studies showed that PLTP enhanced the ability of HDL to promote cholesterol efflux from normal but not Tangier disease fibroblasts (15), implicating the involvement of ABCA1. To further test this idea, we examined the effects of PLTP on cholesterol and phospholipid efflux from J774 murine macrophages expressing low and high levels of ABCA1. To distinguish between different mechanisms of lipid efflux, we incubated cells for 6 h with or without PLTP in the presence of either albumin alone (controls) or albumin plus HDL, tryptsinized HDL (TrHDL), or purified apoA-I. HDL phospholipids promote efflux of cholesterol and, to a lesser extent, phospholipids by ABCA1-independent diffusional mechanisms, whereas HDL apolipoproteins remove cellular cholesterol and phospholipids by the ABCA1 pathway (14). Thus, apolipoprotein-digested TrHDL promotes lipid efflux by diffusion only, purified apoA-I by the ABCA1 pathway only, and HDL by both mechanisms (21, 28).

In the basal state, where ABCA1 levels are very low, HDL and TrHDL promoted cholesterol efflux from macrophages to a greater extent than did apoA-I (Fig. 1A) and had small stimulatory effects on phospholipid efflux (Fig. 1C). The addition of PLTP to these media slightly increased or had no effect on lipid efflux. Thus, when lipid efflux occurs largely by diffusional mechanisms, PLTP has very little lipid efflux activity.

When macrophage ABCA1 was induced by 8-Br-cAMP (26, 29, 30), apoA-I-mediated cholesterol and phospholipid efflux was markedly increased and exceeded that promoted by either HDL or TrHDL (Fig. 1, B and D). With these cells, the addition of PLTP greatly enhanced cholesterol and phospholipid efflux in the presence of HDL or TrHDL but had little effect in the absence of lipid acceptors or in the presence of apoA-I. These results show that PLTP stimulates cholesterol and phospholipid efflux from J774 macrophages by an ABCA1-dependent process, but this occurs only in the presence of phospholipid-rich HDL particles.

To confirm that ABCA1 was involved in the PLTP-enhanced

![Fig. 1. PLTP enhances cholesterol and phospholipid efflux from ABCA1-expressing J774 macrophages in the presence of HDL but not apoA-I. J774 macrophages were incubated for 24 h with 50 μg/ml acetylated LDL followed by 24-h incubations without (Basal) or with (+cAMP) 0.5 mM 8-Br-cAMP, and [3H]cholesterol (A and B) and [3H]choline-labeled phospholipid (C and D) efflux was measured during 6-h incubations with basal or cAMP media containing albumin without or with 10 μg/ml PLTP plus either no additions (Control), 20 μg/ml HDL protein, 20 μg/ml TrHDL, or 10 μg/ml apoA-I. Each value is the mean ± S.D. of triplicate incubations expressed as percentage of total (medium plus cell) radiolabeled free cholesterol or phospholipids.

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Fig. 2. PLTP enhances cholesterol and phospholipid efflux from ABCA1-transfected BHK cells in the presence of HDL but not apoA-I. [3H]Cholesterol (A and B) and [3H]choline-labeled phospholipid (C and D) efflux from mock- and ABCA1-transfected BHK cells was measured during 6-h incubations with medium containing albumin without (−) or with (+) 10 μg/ml PLTP plus either no additions (Control), 20 μg/ml HDL protein, 20 μg/ml TrHDL, or 10 μg/ml apoA-I. Each value is the mean ± S.D. of triplicate incubations expressed as percentage of total (medium plus cell) radiolabeled free cholesterol or phospholipids.

We also measured cholesterol efflux in the presence of the same concentrations of heat-inactivated PLTP or a mutant form of PLTP having −10% normal phospholipid transfer activity (24). Heat-inactivated PLTP completely lacked cholesterol efflux activity, and mutant PLTP had a markedly reduced activity (Fig. 3B). These results show that the PLTP-stimulated cholesterol efflux from ABCA1 transfectants was not simply due to an increase in protein mass but required some structural determinants associated with its phospholipid transfer activity.

We examined the effects of PLTP on ABCA1-mediated cholesterol efflux in the presence of non-HDL phospholipid particles. LDL and phospholipid vesicles stimulated cholesterol efflux from both mock- and ABCA1-transfected BHK cells (Fig. 4). The addition of PLTP to these media enhanced cholesterol efflux from ABCA1-transfected cells (Fig. 4B) but not from mock-transfected cells (Fig. 4A), but the incremental increase was similar to that seen when PLTP was added to control medium alone. Thus, the PLTP effect on ABCA1-dependent lipid efflux appears to have some selectivity for HDL particles.

The above results suggest that the direct interaction of PLTP with ABCA1-expressing cells plays a role in promoting cholesterol efflux. To test this possibility further, we first incubated cells for 4 h with PLTP and then measured cholesterol efflux from washed cells during 2-h incubations without PLTP but with different acceptors. Pretreatment of ABCA1-transfected cells with PLTP significantly increased subsequent cholesterol efflux in the presence of albumin alone (control) or albumin plus either HDL, TrHDL, LDL, or phospholipid vesicles (Fig. 5A). The relative increase was smaller than when PLTP was added directly to the lipoprotein-containing medium, as would be expected if only the small amount of prebound PLTP was enhancing cholesterol efflux. This pretreatment had no effect when ABCA1-transfected cells were subsequently incubated with apoA-I or when mock-transfected cells were incubated with any of these acceptors (Fig. 5B). These results support the concept that the interaction of PLTP with cells rather than with lipoproteins in solution is primarily responsible for the enhanced lipid efflux.
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Fig. 4. PLTP enhances cholesterol efflux from ABCA1-transfected BHK cells in the presence of LDL and phospholipid vesicles. \([^{3}H]\)Cholesterol efflux was measured as described in the legend to Fig. 2 except that the albumin-containing efflux media had either no additions (Control), 20 \(\mu g/ml\) LDL protein, or 20 \(\mu M\) phospholipid vesicles (PLV). Each value is the mean \(\pm\) S.D. of triplicate incubations.

Fig. 5. Pretreating cells with PLTP enhances cholesterol efflux from ABCA1-transfected BHK cells during subsequent incubations. \([^{3}H]\)Cholesterol efflux was measured as described in the legend to Fig. 2 except that cells were first incubated for 4 h without (–) or with (+) 10 \(\mu M\) PLTP, and radiolabeled cholesterol efflux was measured after subsequent 2-h incubations with albumin alone (Control) or albumin plus the indicated acceptors added as described in the legends to Figs. 2 and 3. Each value is the mean \(\pm\) S.D. of triplicate incubations.

high affinity binding sites at 0 °C, and thus most of these sites remain blocked at this temperature during the first several hours after the removal of apolipoproteins (21). This approach has the advantage of minimizing interactions between ligand and competitor in solution, which can give false positive results. Preincubating cells with increasing concentrations of unlabeled apoA-I blocked 80% of the subsequent binding of \(^{125}\)I-PLTP (Fig. 6A), and preincubating cells with increasing concentrations of PLTP blocked 67% of the subsequent binding of \(^{125}\)I-apoA-I (Fig. 6B). These results indicate that PLTP and apoA-I interact with common high affinity binding sites on ABCA1-expressing cells.

To obtain evidence for the functional significance of these binding sites, we tested the effects of increasing concentrations of PLTP on apoA-I-mediated cholesterol efflux from BHK cells. Since PLTP has less ability than apoA-I to promote cholesterol efflux in the absence of HDL (Fig. 2), increasing ratios of PLTP to apoA-I should inhibit cholesterol efflux if saturable common binding sites are involved. Although PLTP had no effect on ABCA1-dependent lipid efflux at similar apoA-I to PLTP mass ratios (10 \(\mu g/ml\) each) (Fig. 2), raising the concentration of PLTP progressively decreased apoA-I-mediated cholesterol efflux from ABCA1-expressing cells (Fig. 6C). A significant inhibition was observed at a PLTP to apoA-I mass ratio of 2.5:1. Thus, the binding sites shared by apoA-I and PLTP appear to play a role in ABCA1-dependent cholesterol transport.

Cross-linking studies have suggested that apoA-I binds directly to ABCA1 (26, 31, 32). We tested whether this is also the case for PLTP by incubating mock- and ABCA1-transfected BHK cells with \(^{125}\)I-PLTP, treating cells with the cross-linking agent DSS, isolating ABCA1 by immunoprecipitation, and detecting \(^{125}\)I-labeled ABCA1 by phosphorimaging of SDS-PAGE gels. Results with ABCA1-transfected cells showed a single iodinated band with an apparent molecular mass greater than 300 kDa that was barely visible in mock-transfected cells and was markedly reduced in intensity when the binding incubations were performed in the presence of a 100-fold excess unlabeled PLTP or apoA-I (Fig. 7A). No band was evident in the absence of DSS (not shown). Excess unlabeled PLTP or apoA-I also blocked cross-linking of \(^{125}\)I-apoA-I to ABCA1 (Fig. 7B). These findings suggest that PLTP and apoA-I bind to ABCA1 by the same or very similar mechanisms.

The interaction of apoA-I with cells stabilizes ABCA1 protein by interfering with its calpain-mediated degradation (33, 34). We examined the possibility that PLTP also stabilizes ABCA1 by comparing the effects of apoA-I and PLTP on the level of ABCA1 protein in J774 macrophages, which were shown previously to have a rapid turnover rate of ABCA1 protein (35). When ABCA1 was induced by cholesterol loading and 8-Br-cAMP treatment, the addition of either apoA-I or PLTP to the cAMP medium for the last 6 h of incubation led to a severalfold increase in the membrane content of ABCA1 (Fig. 8A). When cAMP was removed from the medium during this 6 h, the level of ABCA1 was markedly reduced, consistent with degradation of the preformed protein after the removal of inducer (26). The addition of either apoA-I or PLTP to this medium prevented this reduction in protein, suggesting that they both inhibited ABCA1 degradation.

To confirm that PLTP was affecting ABCA1 protein turnover rather than synthesis, we pulsed cells for 15 min with \(^{35}\)S-methionine after the 6-h incubations, isolated ABCA1 by immunoprecipitation and SDS-PAGE, and compared the relative levels of \(^{35}\)S-labeled ABCA1. The removal of 8-Br-cAMP from the medium decreased incorporation of \(^{35}\)S-methionine into ABCA1 (Fig. 8C), consistent with a reduced transcription of ABCA1 after cAMP removal (26). The addition of PLTP to medium containing or lacking 8-Br-cAMP had no effect on \(^{35}\)S labeling of ABCA1. Thus, PLTP increased ABCA1 levels by stabilizing the protein rather than stimulating protein synthesis.

DISCUSSION

We showed previously that PLTP enhanced HDL-mediated cholesterol efflux from cholesterol-loaded human fibroblasts (15). This enhancement was absent with fibroblasts from a patient with Tangier disease, an HDL deficiency syndrome characterized by an inability of lipid-poor apolipoproteins to remove cellular lipids (36). The subsequent discovery of ABCA1 as the defective gene product in Tangier disease (16–19) implied that this cell transporter as being involved in PLTP-enhanced lipid efflux. Here we confirm that ABCA1 plays a role in this efflux and show that this probably involves a direct interaction of PLTP with ABCA1.
We used two cell models to show that induction of ABCA1 enhances the ability of PLTP to remove cellular cholesterol and phospholipids in the presence of HDL particles. In the basal state, J774 macrophages and BHK cells have a relatively inactive ABCA1 lipid transport pathway, but HDL phospholipids promote efflux of cholesterol and, to a lesser extent, phospholipids by ABCA1-independent diffusional mechanisms. This efflux was unaffected by the addition of PLTP. However, when we induced ABCA1 in macrophages or in ABCA1-transfected BHK cells, PLTP markedly enhanced cholesterol and phospholipid efflux in the presence of HDL particles. Thus, when ABCA1 was induced, PLTP gained the ability to remove cellular cholesterol and phospholipids when co-incubated with phospholipid-rich lipoproteins that promote cholesterol efflux largely by diffusion. In contrast, PLTP had no effect when ABCA1-mediated cholesterol and phospholipid efflux was maximally stimulated by apoA-I.

One difference between these two cell types was that PLTP alone stimulated cholesterol and phospholipid efflux from the ABCA1-transfected BHK cells but not from the cAMP-treated macrophages. Our previous studies also showed that PLTP alone did not promote lipid efflux from cholesterol-loaded fibroblasts (15). These differences may reflect the level of ABCA1 protein expressed in these cells. Our ABCA1-transfected BHK cells contain a 10-fold or higher level of ABCA1 protein compared with either cAMP-treated J774 macrophages or cholesterol-loaded fibroblasts (25). Perhaps PLTP cannot promote lipid efflux from cells in the absence of acceptors below a threshold of ABCA1 expression.

We used two cell models to show that induction of ABCA1 enhances the ability of PLTP to remove cellular cholesterol and phospholipids in the presence of HDL particles. In the basal state, J774 macrophages and BHK cells have a relatively inactive ABCA1 lipid transport pathway, but HDL phospholipids promote efflux of cholesterol and, to a lesser extent, phospholipids by ABCA1-independent diffusional mechanisms. This efflux was unaffected by the addition of PLTP. However, when we induced ABCA1 in macrophages or in ABCA1-transfected BHK cells, PLTP markedly enhanced cholesterol and phospholipid efflux in the presence of HDL particles. Thus, when ABCA1 was induced, PLTP gained the ability to remove cellular cholesterol and phospholipids when co-incubated with phospholipid-rich lipoproteins that promote cholesterol efflux largely by diffusion. In contrast, PLTP had no effect when ABCA1-mediated cholesterol and phospholipid efflux was maximally stimulated by apoA-I.

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These results suggest that the lipid efflux activity of PLTP was not a simple mass effect and required some structural determinants related to its phospholipid transfer activity.

The most likely explanation for the above findings is that PLTP interacts with cells and removes lipids by the ABCA1 pathway. In support of the role of cellular interactions are results showing that PLTP had the same cholesterol efflux stimulatory pattern, although to a lesser extent, when ABCA1-transfected cells were first treated with PLTP alone and then incubated with PLTP-free medium containing different lipid acceptors. Because of its low lipid binding capacity compared with apolipoproteins, PLTP may require acceptor particles to act as sinks for the lipids it transports from cells. This would explain why PLTP had a greater ability to stimulate lipid efflux when co-incubated with HDL particles. PLTP plus HDL or TrHDL removed cholesterol and phospholipids from ABCA1-expressing cells to the same or a greater extent than did apoA-I. Although PLTP also enhanced cholesterol efflux from ABCA1-transfected cells when added to medium containing LDL or phospholipid vesicles, the increase was similar to that seen when PLTP alone was added to particle-free medium. This suggests that HDL particles are the preferred recipients of PLTP-transported cellular lipids.

Although the lipid transport requirements may differ, apoA-I and PLTP appear to share common mechanisms for interacting with ABCA1-expressing cells and with ABCA1 itself. ABCA1 induction in BHK cells dramatically increased cell surface binding of both apoA-I and PLTP, and cross-competition experiments showed that most of this binding was to common sites. As shown previously for apoA-I (26, 31, 32), 125I-labeled PLTP covalently attached to ABCA1 when cells were treated with the cross-linking agent DSS, indicating that PLTP comes in close proximity (<1.2 nm) to ABCA1 on cells. Excess unlabeled PLTP and apoA-I blocked cross-linking of both 125I-PLTP and 125I-apoA-I to ABCA1, consistent with these molecules interacting with the same or closely associated sites on ABCA1.

Last, we found that the addition of both apoA-I and PLTP blocked the degradation of cAMP-induced ABCA1 that follows the removal of inducer from the medium. Thus, PLTP mimics apoA-I in its ability to stabilize ABCA1 (33, 34), which is presumably due to direct binding to ABCA1.

It is unclear what common properties of apoA-I and PLTP mediate their interactions with ABCA1-expressing cells. Studies with synthetic peptides implicate amphipathic H11021-263. It is possible that H11200-263 in PLTP mimic those in apolipoproteins in their -helices with amphipathic proper-...
