Janus Kinase 2 Modulates the Apolipoprotein Interactions with ABCA1 Required for Removing Cellular Cholesterol*

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ABCA1 Required for Removing Cellular Cholesterol*

Population studies have shown an inverse relationship between plasma high density lipoprotein (HDL)1 levels and risk for cardiovascular disease, implying that factors associated with HDL metabolism are atheroprotective. One of these factors is a cell membrane transporter called ABCA1, which mediates the transport of excess cholesterol from cells to HDL apolipoproteins (1, 2). ABCA1 mutations can cause Tangier disease (3, 4), a severe HDL deficiency syndrome characterized by cholesterol deposition in tissue macrophages and prevalent atherosclerosis (5–7). Genetic manipulations of ABCA1 expression in mice also affect plasma HDL levels and atherogenesis (8, 9).

The cell membrane content of ABCA1 is highly regulated by transcriptional and post-translational processes (1, 2). ABCA1 transcription is induced by sterols through activation of nuclear liver X receptors (LXRs) (10, 11). ABCA1 protein is destabilized by specific proteases (12), unsaturated fatty acids (13), and cytotoxic levels of intracellular cholesterol (14) and is stabilized by apolipoproteins (2, 15).

There is emerging evidence that multiple signaling events play a role in controlling ABCA1 protein levels and activity. It has been shown that protein kinase A (PKA)-mediated phosphorylation of ABCA1 is essential for optimum lipid transport activity (16) and that apolipoproteins can enhance their ability to remove cellular cholesterol by activating this signaling pathway (17). ABCA1 contains a cytosolic PEST sequence that, when phosphorylated, directs calpain-mediated proteolysis of ABCA1 (12, 18). The interaction of apolipoproteins with cells prevents this PEST phosphorylation and thus stabilizes ABCA1 (18). Removal of sphingomyelin by apolipoproteins has been reported to activate protein kinase C, which in turn phosphorylates and stabilizes ABCA1 (19).

These studies implicate apolipoprotein interactions with cells as initiating ABCA1-modulating signaling events. The nature of these interactions is poorly understood. Cross-linking experiments have shown that apolipoproteins interact directly with ABCA1 on the cell surface (20–22). This interaction appears to be essential for removal of cellular lipids but is not sufficient, as some mutations in ABCA1 impair lipid efflux without affecting apolipoprotein binding to cells or to ABCA1 (16, 22). It is unknown if direct binding of apolipoproteins to ABCA1 activates signaling pathways.

In the current study, we investigated the role of different signaling pathways in modulating ABCA1 activity. We found that, in addition to PKA, the protein-tyrosine kinase Janus kinase 2 (JAK2) is required for optimum ABCA1-dependent transport of lipids from cells to apolipoproteins. Unlike PKA, which affects the lipid transport activity of ABCA1 without affecting apolipoprotein binding, JAK2 appears to selectively modulate the apolipoprotein interactions with ABCA1 required for lipid removal. Results showing that apolipoprotein A-I (apoA-I) stimulates JAK2 autophosphorylation reveal a novel mechanism by which apolipoproteins potentiate their ability to remove excess cholesterol from cells.

EXPERIMENTAL PROCEDURES

Cell Culture and Cellular Proteins—Baby hamster kidney (BHK) cells expressing mifepristone-inducible human ABCA1 were generated as described previously (23). ABCA1 was induced to high levels during

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3 The abbreviations used are: HDL, high density lipoprotein; ABCA1, ATP-binding cassette transporter A1; DMEM, Dulbecco’s modified Eagle’s medium; BSA, bovine serum albumin; BHK, baby hamster kidney; LXRs, liver X receptors; PKA, protein kinase A; TK, tyrosine kinase; JAK2, Janus kinase 2; 8-Br-cAMP, 8-bromo-cAMP.
6–24-h incubations with DMEM containing 1 mg/ml bovine serum albumin (DMEM/BSA) and 10 ng/ml mifepristone (23). Mutant γ2A cells lacking JAK2 (a gift from Dr. George R. Stark) were generated from wild-type 2C4 fibrosarcoma cells as described (24, 25). ABCA1 was induced in γ2A and 2C4 cells by 18–20-h incubations with DMEM/BSA containing 10 μM 22(R)-hydroxycholesterol plus 10 μM 9-cis-retinoic acid (13). Cellular contents of ABCA1, JAK2, and phosphorylated JAK2 were measured by immunoblot analyses using antibodies to ABCA1 (23), JAK2 (Santa Cruz Biotechnology), and tyrosine-phosphorylated JAK2 (BIO SOURCE International). Cell-surface ABCA1 was measured by treating cells for 30 min at room temperature with 1 mg/ml sulfob-NHS-biotin, isolating ABCA1 by immunoprecipitation and SDS-PAGE, and probing nitrocellulose blots with a streptavidin-horseradish peroxidase ECL assay (Bio-Rad) (13, 20).

**Lipid Efflux—Cellular cholesterol was labeled with 1 μCi/ml [3H]cholesterol (PerkinElmer Life Sciences) added to the growth medium 24 h prior to a 20-h incubation ± mifepristone (BHK cells) or ± 22(R)-hydroxycholesterol/9-cis-retinoic acid (fibrosarcoma cells), and cellular phospholipids were labeled with 1 μCi/ml [3H]choline chloride (Amersham Biosciences) added during the induction incubations (23). Washed cells were then incubated with the indicated kinase inhibitors for 6–6 h in DMEM/BSA followed by 1.5-h incubations in the same media minus or plus 5 μg/ml apoA-I, and medium and cells were assayed for either free [3H]cholesterol or [3H]choline-labeled phospholipids (13, 23). For ABCA1-induced cells, inducers were added to the treatment and efflux media. ApoA-I-mediated lipid efflux was calculated as the percent total [3H]-lipid released into medium after subtraction of values obtained in the absence of apoA-I. For the experiments shown, the mean [3H]cholesterol and [3H]phospholipid content of cells was 84,250 and 69,976 cpm/well, respectively. The mean fractional cholesterol and phospholipid effluxes for the 1.5-h incubations were 3.3 ± 2.6%, respectively.

**Cell-surface and ABCA1 Binding of ApoA-I—**For the whole-cell binding assay, cells were incubated for 2 h at 0 °C with 1 μg/ml (BHK cells) or 10 μg/ml (fibrosarcoma cells) 125I-apoA-I ± 200 μg/ml unlabeled apoA-I, and cell-associated radioactivity and cell protein were measured in 0.2 N NaOH digests of washed cells (23). Results are expressed as nanograms of apoA-I per mg of cell protein after subtraction of values in the presence of unlabeled apoA-I. For the ABCA1 binding studies, cells were incubated with 5 μg/ml 125I-apoA-I for 2 h, treated for 30 min at room temperature with PBS containing 1 mg/ml DSS (cross-linking agent), and washed twice with cold PBS containing 20 mM glycine (13, 20). ABCA1 was isolated from detergent extracts by immunoprecipitation and SDS-PAGE, and 125I-ApoA-I was visualized by Phosphorimaging.

**ABCA1-dependent Cholesterol Redistribution—**[3H]Cholesterol-labeled ABCA1-transfected cells were incubated for 6 h ± mifepristone ± 5 μg/ml apoA-I and the indicated inhibitor, and [3H]cholesterol-labeled fibrosarcoma cells were incubated for 18 h ± 22(R)-hydroxycholesterol/9-cis-retinoic acid. Cholesterol efflux was measured as the fraction of [3H]cholesterol appearing in the medium, and redistribution of cellular cholesterol was determined by treating washed cells for 15 min with 1 unit/ml cholesterol oxidase and measuring conversion of [3H]cholesterol to [3H]cholestene (23).

**ABCA1 Phosphorylation—**Cells were incubated with phosphate-free/BSA containing [32P]orthophosphate (0.5 μCi per 60-mm plate) for 2 h to label the endogenous adenosine triphosphate pool (26) followed by 3-h incubations with DMEM/BSA containing the indicated additions. ABCA1 was isolated by immunoprecipitation and SDS-PAGE, and 32P-ABCA1 was visualized by autoradiography. ABCA1 phosphoserines and phosphothreonines were assayed by immunoblot analysis of isolated ABCA1 using antibodies specific for these sites.

**Dominate-negative JAK2 Transfection—**Mifepristone-treated cells were radiolabeled overnight with [3H]cholesterol and then transfected with 2 μg/well dominant-negative JAK2 (a gift from Dr. Ralph B. Arlinghaus) or the empty PK5 vector using transfection reagent PUGENE 6 (Roche Applied Science) as described by the manufacturer. Cholesterol efflux was measured 36 h after transfection.

**RESULTS**

**PKA and JAK2 Inhibitors Suppress ABCA1 Activity by Different Mechanisms—**To identify phosphorylation events that may be involved in ABCA1 function, we tested the effects of PKA, protein kinase C, and TK inhibitors on different ABCA1 activity parameters. To avoid the complications of altered ABCA1 transcription, we used a BHK cell line stably transfected with a mifepristone-inducible ABCA1 cDNA (23). The PKA inhibitor H89 significantly decreased cholesterol and phospholipid efflux from ABCA1-expressing cells to apoA-I (Fig. 1, a and b) without altering apoA-I binding to cells (Fig.
ABCA1-transfected BHK cells with a dominant-negative JAK2 activity but by different mechanisms. 

With near maximum effects occurring at 100, 40, and 40 μM-mediated cholesterol efflux were concentration-dependent, to cells (Fig. 1)—apoA-I-mediated lipid efflux (Fig. 1, a, AG490, and H89). Daidzein, an inactive analog of genistein, or the protein kinase C inhibitor GF109203X had no significant effect (not shown). Daidzein, an inactive analog of genistein, or the protein kinase C inhibitor GF109203X had no stimulatory effect on these parameters, consistent with endogenous levels of cAMP being sufficient for maximum ABCA1 activation by PKA.

We found that the broad spectrum TK inhibitor genistein and the JAK2-specific TK inhibitor AG490 also markedly decreased apoA-I-mediated cholesterol and phospholipid efflux from ABCA1-expressing cells (Fig. 1, a and b) but, in contrast to H89, genistein and AG490 also suppressed apoA-I binding to cells (Fig. 1d) and to ABCA1 (Fig. 1e). These effects do not appear to be cell-specific, as genistein and AG490 inhibited ABCA1-dependent cholesterol and phospholipid efflux from non-transfected, cholesterol-loaded murine J774 macrophages (not shown). Daidzein, an inactive analog of genistein, or the protein kinase C inhibitor GF109203X had no significant effect on apoA-I-mediated lipid efflux from ABCA1 transfectants (Fig. 1, a and b). Moreover, the SRE family TK inhibitor 4-amino-5-(4-methylphenyl)-7-(t-butyl)pyrazolo-3,4-d-pyrimidine or the epidermal growth factor receptor TK inhibitor tyrphostin-23 had no effect on apoA-I-mediated lipid efflux (Fig. 1, a and b) or apoA-I binding to cells (Fig. 1d) or to ABCA1 (Fig. 1e). Transient transfection of ABCA1-transfected BHK cells with a dominant-negative JAK2 cDNA significantly suppressed apoA-I-mediated cholesterol efflux (Fig. 1c). These results indicate that both PKA and JAK2 modulate ABCA1 activity but by different mechanisms.

The inhibitory effects of genistein, AG490, and H89 on apoA-I-mediated cholesterol efflux were concentration-dependent, with near maximum effects occurring at 100, 40, and 40 μM, respectively (Fig. 2a). We compared time courses for these inhibitory effects by preincubating cells for various times with inhibitors and measuring apoA-I-mediated cholesterol efflux during subsequent 1.5-h incubations. Both genistein and AG490 significantly decreased cholesterol efflux without preincubation, having their maximum effects during the 1.5-h incubation with apoA-I (Fig. 2b). In contrast, H89 did not significantly decrease apoA-I-mediated cholesterol efflux until after a 2-h preincubation and did not reach maximum inhibition until after a 5-h preincubation (Fig. 2b). Thus, ABCA1-dependent cholesterol efflux is more acutely sensitive to JAK2 inhibition than to PKA inhibition.

**PKA but Not JAK2 Inhibition Suppresses ABCA1 Cholesterol Translocase Activity**—We showed previously (23) that induction of ABCA1 in transfected BHK cells redistributes cholesterol to cell-surface sites accessible to the added enzyme cholesterol oxidase. Here we compared the effects of JAK2 and PKA inhibition on this redistribution. With radiolabeled cells deficient in ABCA1, about 6% of the [3H]cholesterol was converted to [3H]cholestenone by treating cells for 15 min with cholesterol oxidase (Fig. 3a), and this as well as cholesterol efflux (Fig. 3c) was unaffected by 6-h preincubations with apoA-I, AG490, or H89. Incubating cells with mifepristone for 6 h to induce ABCA1 prior to the oxidase treatment led to a greater than 2-fold increase in redistribution of [3H]cholesterol to oxidase-accessible sites (Fig. 3b). Including apoA-I in the medium during the 6-h induction phase reduced this redistribution in association with removal of [3H]cholesterol from cells (Fig. 3d).

Inducing ABCA1 in the presence of AG490 redistributed a nearly normal amount of [3H]cholesterol to oxidase-accessible sites (Fig. 3b), despite a reduced ability of apoA-I to remove this cholesterol (Fig. 3d). Thus, most of the effects of the JAK2 inhibitor could not be attributed to an impaired intrinsic cholesterol translocase activity of ABCA1. In contrast, the ABCA1-mediated redistribution of [3H]cholesterol to oxidase-accessible pools was reduced by over 60% in the presence of H89 (Fig. 3b), consistent with PKA inhibition having a direct effect on this process. These data along with those in Fig. 1 suggest that, whereas H89 selectively impairs ABCA1 lipid transport activity, JAK2 selectively modulates the apolipoprotein interactions with ABCA1 required for removing lipids from cells.

**PKA or TK Inhibition Had No Effect on ABCA1 Protein Levels**—Immunoblot analysis of whole cells revealed that treating cells for 3 h with either 8-Br-cAMP, H89, genistein (Fig. 4a), or AG490 (not shown) had no effect on the cellular content of ABCA1. Biotinylation of cell-surface proteins and isolation of ABCA1 by immunoprecipitation showed that none of these treatments affected the cell-surface distribution of ABCA1 (Fig. 4a). Both PKA and JAK2 therefore modulate ABCA1 activity without directly affecting protein expression or trafficking to the plasma membrane.

**PKA but Not TK Inhibition Reduces ABCA1 Phosphorylation**—We measured the effects of PKA and TK inhibition on the relative degree of ABCA1 phosphorylation by labeling cells with [32P]orthophosphate and isolating ABCA1 by immunoprecipitation. To test the possibility that these inhibitors affect apoA-I-mediated ABCA1 phosphorylation (17–19), apoA-I was added to the medium during the last 30 min of the 3-h treatments. Blots showed a single [32P]-labeled band with a molecular mass of ~240 kDa in ABCA1-transfected cells but not in mock-transfected cells (Fig. 4b), consistent with the previously reported constitutive phosphorylation of ABCA1 (16, 18). This phosphorylation was unaffected by short-term treatments with apoA-I. ABCA1 phosphorylation was significantly decreased by the PKA inhibitor H-89 but not by the TK inhibitors genistein (Fig. 4b) or AG490 (not shown). Consistent with the efflux data, the phosphorylation state of ABCA1 was not increased further by the PKA activator 8-Br-cAMP. These data suggest that PKA but not TK contribute to the constitutive phosphorylation of ABCA1.

To examine further if ABCA1 tyrosines are phosphorylated, we isolated intact ABCA1 from cells by immunoprecipitation and SDS-PAGE and performed immunoblot analyses with phosphoserine- and phosphotyrosine-specific antibodies. Although phosphoserines in ABCA1 were readily detectable, we were unable to detect any signal for phosphotyrosines (data not shown). We were also unable to identify ABCA1 among membrane proteins immunoprecipitated with a phosphotyrosine-
specific antibody. These results suggest that ABCA1 is not phosphorylated by TKs and implicate another JAK2-targeted protein in the ABCA1 pathway.

**ABCA-dependent Lipid Removal Is Impaired in Cells Lacking JAK2**—We examined the effects of a total absence of JAK2 on ABCA1 function by comparing parameters of ABCA1 activity between wild-type 2C4 fibrosarcoma cells and a mutant 2C4 cell line that lacks JAK2 mRNA and protein (H92532A cells) (25). In the basal state, both the wild-type 2C4 and mutant γ2A cells had nearly undetectable levels of ABCA1 protein (Fig. 5a). Treating these two cell lines with the LXR ligand 22(R)-hydroxycholesterol plus the retinoid X receptor ligand 9-cis-retinoic acid induced ABCA1 to comparable levels (Fig. 5a). These ligands also increased apoAI-mediated cholesterol (Fig. 5c) and phospholipid (Fig. 5d) efflux, apoAI binding to cells (Fig. 5e), and apoAI cross-linking to ABCA1 (Fig. 5f), but these were markedly reduced in mutant γ2A cells compared with wild-type 2C4 cells. As with ABCA1-transfected BHK cells, induction of ABCA1 in both of these cell lines increased the cholesterol fraction accessible to cholesterol oxidase treatment, and this was only slightly lower in γ2A cells lacking JAK2 (Fig. 5f). Thus, although a lack of JAK2 has little effect on ABCA1 expression or intrinsic cholesterol translocase activity, it severely impairs apolipoprotein-ABCA1 interactions and lipid removal.

**ApoAI Stimulates JAK2 Autophosphorylation**—Cytokine-induced activation of JAK2 has been shown to involve autophosphorylation of JAK2 (27). We therefore tested the effects of apoAI on the phosphorylation state of JAK2 by immunoblot analysis with a phosphospecific JAK2 antibody. Acute treatment (15 min) of ABCA1-deficient cells with either apoAI or AG490 had little effect on the total or phosphorylated amounts of JAK2 (Fig. 6). However, apoAI treatment of ABCA1-expressing cells markedly increased the amount of phosphorylated JAK2 without affecting the total amount of JAK2 (Fig. 6). This increase was largely prevented when cells were preincubated with the JAK2 inhibitor AG490, indicating that it mostly involved an autophosphorylation mechanism. Thus, the interaction of apoAI with cells acutely stimulates autophosphorylation of JAK2 by an ABCA1-dependent process.
DISCUSSION

The current study provides several lines of evidence that the non-receptor TK JAK2 modulates ABCA1-dependent lipid transport from cells to HDL apolipoproteins. First, treatment of ABCA1-transfected BHK cells with the broad spectrum TK inhibitor genistein or the JAK2-specific TK inhibitor AG490 greatly suppressed apoA-I-mediated cholesterol and phospholipid efflux. Second, dominant-negative JAK2 transfection of these cells significantly decreased apoA-I-mediated cholesterol efflux. Third, apoA-I had a severely impaired ability to remove cholesterol and phospholipids from a mutant cell line that lacks JAK2. These studies show that JAK2 activity and expression are required for optimum ABCA1-dependent transport of cellular lipids to apolipoproteins.

Additional evidence suggests that JAK2 selectively modulates the apolipoproteins-ABCA1 interactions required for lipid removal. The inhibitory effects of genistein and AG490 on lipid efflux were associated with a similar degree of inhibition of apoA-I binding to ABCA1-expressing cells and covalent cross-linking of apoA-I to ABCA1. These inhibitors had no effect on the plasma membrane content of ABCA1, and AG490 had only a small, insignificant effect on the intrinsic cholesterol translocase activity of ABCA1 as determined by cholesterol oxidase accessibility. We observed a similar pattern when mutant γ2A
deficient (and reprobed with a total JAK2 antibody. Blots represent 4 experiments. Ctrl, control.

cells lacking JAK2 were compared with the parental wild-type 2C4 cells. Thus, apoA-I interactions with ABCA1 and lipid efflux to apoA-I were substantially impaired by inhibiting or abolishing JAK2, whereas ABCA1 protein levels were unaffected, and ABCA1 cholesterol translocase activity was only slightly reduced. The most likely explanation for these findings is that JAK2 promotes apolipoprotein interactions with ABCA1 or a closely proximal site, and this facilitates the removal of cellular lipids.

A comparison of TK inhibitors suggests that most if not all the effects of genistein could be attributed to JAK2 inhibition. Genistein and AG490 inhibited lipid efflux and apolipoprotein binding to similar extents. The effects of both inhibitors were rapid, causing near maximum inhibition when added to the medium during the 1.5-h cholesterol efflux assay. Moreover, inhibitors of SRC family or epidermal growth factor receptor TKs had no effect on ABCA1 activity. These studies, however, do not exclude the possibility that another genistein-sensitive TK also influences ABCA1 activity.

We used the PKA inhibitor H89 as a positive control for our studies, as it was reported previously that PKA-mediated phosphorylation of ABCA1 was required for its lipid transport activity (16). We confirmed that PKA inhibition reduces apoA-I-mediated cholesterol and phospholipid efflux from ABCA1-expressing cells without affecting apoA-I binding to these cells. We also show that PKA inhibition has no effect on apoA-I-mediated cholesterol and phospholipid efflux from ABCA1-expressing cells without affecting apoA-I binding to these cells. This binding is required for removal of cholesterol and phospholipids from cells and may play a role in stabilizing ABCA1 protein. JAK2 activation may involve the interaction of apolipoproteins with either ABCA1 itself, an unidentified receptor, or membrane lipids. A lack of detectable phosphotyrosines in ABCA1 implies that the JAK2-targeted protein is not ABCA1 but some other protein that promotes apolipoprotein-ABCA1 interactions. The inability of apoA-I to stimulate ABCA1 phosphorylation when JAK2 is activated also supports this assumption. It would be of great interest to identify these molecules, as they are obviously important regulated components of this atheroprotective pathway.

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