A Drosophila Microsomal Triglyceride Transfer Protein Homolog Promotes the Assembly and Secretion of Human Apolipoprotein B

IMPLICATIONS FOR HUMAN AND INSECT LIPID TRANSPORT AND METABOLISM*

The assembly and secretion of triglyceride-rich lipoproteins in vertebrates requires apolipoprotein B (apoB) and the endoplasmic reticulum-localized cofactor, microsomal triglyceride transfer protein (MTP). Invertebrates, particularly insects, transport the majority of their neutral and polar lipids in lipophorins; however, the assembly of lipophorin precursors was presumed to be MTP-independent. A Drosophila melanogaster expressed gene sequence (CG9342), displaying 23% identity with human MTP, was recently identified. When coexpressed in COS cells, CG9342 promoted the assembly and secretion of apoB34 and apoB41 (N-terminal 34 and 41% of human apoB). The apoB34-containing particles assembled by human MTP and CG9342 displayed similar peak densities of 1.169 g/ml and similar lipid compositions. However, CG9342 displayed differential sensitivities to two inhibitors of human MTP and low lipid compositions. This paper is available online at http://www.jbc.org

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Processes responsible for the efficient capture, transport, and storage of lipids are observed in all multicellular organisms. In vertebrates, apoB plays a complex role in lipid utilization, beginning with the enterocytic assembly of dietary lipids to form chylomicron particles (1). The liver is the second major site of apoB expression where it assembles endogenous lipids to form triglyceride (TG)-rich very low density lipoproteins (VLDL) (2). Both chylomicrons and VLDL function to distribute TG to peripheral tissues; however, metabolic products of these particles can accumulate in plasma and contribute to several chronic disease states, including atherosclerosis and diabetes (3, 4). The discovery of MTP as a critical cofactor essential for chylomycin and VLDL formation has provided considerable mechanistic insight into the processes responsible for intracellular lipoprotein assembly (5–7). However, many aspects of this pathway remain elusive.

An important clue for understanding lipoprotein assembly is the notion, first introduced in 1988, that apoB is a distant relative of vitellogenin (8). It was subsequently noted that MTP is also a member of this gene family (9) and that the greatest similarity among vitellogenin, apoB, and MTP is concentrated within their amino-terminal —750 to 1000 amino acids (10–12). Vitellogenin is an ancient lipid-binding protein that functions in the transport of lipids and other nutrients (13) from liver or fat body to the developing oocyte of oviparous vertebrates and invertebrates (14, 15). Another form of primitive lipoprotein biogenesis is the assembly of apolipopophorin II/I (apoLp-II/I) into high density lipoporphin (HDLp) particles (16, 17). Unlike apoB-containing particles, whose initial formation and ongoing enlargement occurs exclusively within the secretory pathway, maturation of HDLp is a post secretory event that is achieved by efflux of diglycerides from insect fat body to the HDLp acceptor. The mature lipophorin, termed low density lipopophorin, is then delivered to flight muscle where its lipid is discharged and used as an energy source. Although apoLp-II/I is also a homolog of apoB (18), the fat body cell-dependent assembly of HDLp, and primitive lipoprotein assembly in general, were presumed to be MTP-independent (16, 19).

More comprehensive searches for MTP-like proteins in insects were made possible by the recent completion of several insect genome projects, including that of Drosophila melanogaster (20) and Anopheles gambiae (21). When the Drosophila data base was searched for sequences similar to human MTP a single gene, CG9342, was identified. Given its 23% identity with human MTP, this gene product was initially described as a triglyceride-binding protein (22). In this report we functionally characterized CG9342 and observed that, in transfected cells, it supports the assembly and secretion of human apoB34 and apoB41 as lipoprotein precursors. In addition, we observed functional and structural differences between CG9342 and human MTP, possibly reflecting known differences in intracellular and extracellular aspects of vertebrate and invertebrate lipid transport and metabolism. The identification of invertebrate orthologs of human MTP may enable structural and functional dissection of the multiple roles of human MTP in apoB assembly as well as apoB-independent effects on intracellular lipid trafficking (23–25).
EXPERIMENTAL PROCEDURES

Sequence Alignments—MTP sequences were aligned with the ClustalW multiple sequence alignment tool using the BLOSUM 30 matrix and implemented in MacVector (BioLabs, Inc., Sene). Some records used were as follows: Homo sapiens (human): locus, MTP_HUMAN; GenBankTM accession number, P55157. Bos taurus (bovine): locus, A46764; accession number, A4764. Mus musculus (mouse): MTP: locus, MTP; accession, NP_032668. Fugu rubripes (puffer fish): Copyright definition, SINIRUP0000008905, D. melanogaster fruit fly: locus, CG9342; accession number, NP_1100075. Anguilla japonica (mosquito): locus, EAA13951; accession number, EAA14951. Signal peptide cleavage sites for the Fugu and Drosophila sequences were predicted using the SignalP prediction algorithm (26) as implemented by the SignalP V2.0 server on the web. The amino terminus of mature human MTP was based on data reported by Shoulders et al. (27). The full-length EST for D. melanogaster CG9342 cloned into the vector, pOT2, was obtained from ResGen (Invitrogen). For expression in COS cells, the CG9342 cDNA was transferred to expression vector pcMV5 (28). ApoB34H (amino-terminal 34% of apoB with a carboxyl-terminal peptidase cleavage sites for the locus, CG9342; accession number, NP_610075.

RESULTS

Alignment of CG9342 with Vertebrate MTPs—The deduced amino acid sequence of CG9342 was compared with human and Fugu MTP (Fig. 1). The human and lower vertebrate (Fugu) sequences shared 55% identity/72% similarity over a 882-amino acid alignment, with one gapped region. The Drosophila sequence displayed 23% identity/42% similarity with human MTP and 22% identity/41% similarity with Fugu MTP, each over a 902-amino acid alignment containing 22 gapped regions. Hence, the identity between higher and lower vertebrate MTP is substantial, suggesting analogous functional roles. However, the considerably lower identity between the insect and vertebrate sequences, coupled with different lipid transport mechanisms observed across these species (16), makes the assignment of Drosophila CG9342 function difficult based on sequence comparison alone.

CG9342 Induces the Secretion of ApoB—A functional hallmark of MTP is its capacity to induce the secretion of apoB (36–38). To explore whether CG9342 encodes a functional MTP, it was transiently expressed along with human apoB34 in COS cells. ApoB34 is incapable of undergoing appreciable secretion into media (M) in the absence of MTP (Fig. 2, lane 2). Cotransfection with human MTP dramatically induced apoB34 secretion (lane 4). CG9342 also induced apoB34 secretion, although with slightly lower efficiency (lanes 6 and 8). Another hallmark of MTP is its capacity to interact physically with apoB (10, 39–41). As observed in immunoprecipitates of cell extracts (C), both human MTP (lane 3) and CG9342 (lanes 5 and 7) appear to communoprecipitate with apoB34. It has been known for some time that human MTP migrates more rapidly during SDS-PAGE than predicted from its calculated molecular weight (5), which may explain the relatively slower migration of Drosophila CG9342.

CG9342 Promotes the Secretion of ApoB34 as a Buoyant Lipoprotein Particle with a Density and Lipid Composition Similar to That Produced by Human MTP—To directly assess whether the Drosophila protein is capable of assembling apoB34 with lipid, apoB34 was cotransfected into COS cells with either human MTP or CG9342. After radiolabeling with [35S]Met/Cys, media was subjected to density gradient centrifugation and apoB was recovered by immunoprecipitation. ApoB34 displayed a relatively heterogeneous density distribution profile with a peak of ~1.169 g/ml (Fig. 3). This value is in

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agreement with density values obtained by others in stably transfected McA-RH7777 rat hepatoma cells (42). The composition of lipids associated with apoB34 was explored by radio-labeling transfected cells with \([3H]\)oleate. After affinity purification of the apoB34-containing particles, lipids were separated by TLC and quantified by liquid scintillation counting. As observed in Fig. 4, the relative composition of \([3H]\)oleate-labeled lipids associated with apoB34-containing particles secreted from COS cells cotransfected with either human MTP or \(Drosophila\) CG9342 was virtually identical.

**CG9342 and Human MTP Display Differential Susceptibilities to Chemical Inhibitors of Vertebrate MTP**—To further explore whether the CG9342 gene product displays properties consistent with the behavior of vertebrate MTP, we tested its response to two well-characterized MTP inhibitors. Cells were cotransfected with apoB41 or apoB6.6 and either AP, human MTP, or CG9342. Twenty-four hours after transfection, cells were radiolabeled with \([35S]\)Met/Cys in the presence of 0–20 \(\mu\)M BMS-200150 for 5 h (33, 43). Cell lysate and media samples were subjected to immunoprecipitation with anti-apoB100 antibodies and analyzed by SDS-PAGE and fluorography. As expected, BMS-200150 inhibited the secretion of apoB41 from human MTP transfected cells in a dose-dependent manner (Fig. 5, top panel). Secretion of apoB41 from CG9342-expressing cells was also inhibited to a similar
secreted by human MTP- and CG9342-cotransfected cells. Radiolabeled lipid composition for the apoB34-containing lipoproteins from two, 150-mm dishes, were used to calculate an average percent values from duplicate samples, each consisting of particles purified with an IC50 of 2500 nM BMS-197636 for 20 h. The concentration range of inhibitor was extended to 2500 nM BMS-197636 for 20 h. Media samples were then analyzed for relative apoB41F content by ELISA. Each bar represents the average of duplicate experiments normalized to cell protein and expressed as a percentage of secretion observed in untreated cells. Error bars depict the data range.

secretion from CG9342-transfected cells (Fig. 6B, right panel). ApoB6.6 secretion was unaltered under these conditions (data not shown).

**Fig. 4.** ApoB34-containing particles formed by human MTP or CG9342 display similar lipid compositions. COS-1 cells in 150-mm dishes were transfected by the DEAE-dextran method with apoB34H and either human MTP (hMTP, hatched bars) or CG9342 (unshaded bars). Forty hours after transfection, cells were labeled with [35S]Met/Cys and [3H]oleate for 24 h. ApoB34H was purified from media by nickel chromatography and [3H]oleate-labeled phosphatidycholine (PC), diacylglycerol (DG), triglyceride (TG), and cholesteryl ester (CE) were quantified by TLC and liquid scintillation counting. The values from duplicate samples, each consisting of particles purified from two, 150-mm dishes, were used to calculate an average percent radiolabeled lipid composition for the apoB34-containing lipoproteins secreted by human MTP- and CG9342-cotransfected cells. Error bars, where visible, depict the data range.

**Fig. 5.** ApoB41 secretion from both human MTP- and Drosophila CG9342-transfected cells is inhibited by BMS-200150. COS cells in six-well plates were transfected with apoB41F (B41) or apoB6.6F (B6.6) and AP, human MTP (hMTP), or CG9342, as indicated. Cells were radiolabeled with [35S]Met/Cys for 5 h in the presence of 0–2500 nM BMS-200150. Following labeling, cell lysate (C) and media (M) samples were immunoprecipitated with anti-apoB100 antibodies and analyzed by SDS-PAGE and fluorography.

The inhibition profile of CG9342 was further explored using BMS-197636, a more potent inhibitor of MTP (34). In the human MTP-expressing cells there was a dose-dependent decrease in apoB41 secretion (Fig. 6A, upper panel). However, no inhibition of apoB41 secretion was observed in the CG9342-transfected cells, even at the highest concentration of BMS-197636 used (middle panel). As expected, BMS-197636 had no effect on apoB6.6 secretion (lower panel). To verify these results an additional set of transfected cells were incubated in duplicate with media containing 0–2500 nM BMS-197636 for 20 h. The concentration range of inhibitor was extended to determine whether a higher dose of inhibitor was needed to perturb apoB41 secretion from CG9342-transfected cells. Media were analyzed by ELISA for apoB41 mass, as described (29). As with the short term radiolabeling studies, the secretion of apoB41 from human MTP-transfected cells was inhibited with an IC50 of 50 nM (Fig. 6B, left panel). However, BMS-197636 concentrations of up to 2500 nM had no effect on apoB41 secretion from CG9342-transfected cells (Fig. 6B, right panel). ApoB6.6 secretion was unaltered under these conditions (data not shown).

**Fig. 6.** CG9342-dependent secretion of apoB34 is resistant to the human MTP inhibitor, BMS-197636. COS cells in six-well plates were transfected with apoB41F (B41) or apoB6.6F (B6.6) and AP, human MTP (hMTP), or CG9342, as indicated. A, cells were labeled with [35S]Met/Cys for 5 h in the presence of 0–1250 nM BMS-197636. Cell lysate (C) and media (M) samples were immunoprecipitated with anti-apoB100 antibodies and analyzed by SDS-PAGE and fluorography. In B, duplicate wells of cells were treated with 0–2500 nM BMS-197636 for 20 h. Media samples were then analyzed for relative apoB41F content by ELISA. Each bar represents the average of duplicate experiments normalized to cell protein and expressed as a percentage of secretion observed in untreated cells. Error bars depict the data range.

**Functional Characterization of a Drosophila MTP Homolog**

A structural feature of human MTP-mediated lipid transfer—A structural feature of human MTP is the presence of two hydrophobic peptides important for membrane binding and lipid transfer activity (45). One of these peptides (peptide A) is predicted to associate with membrane surfaces at an oblique angle, destabilizing the bilayer and facilitating lipid acquisition (45). Interestingly, however, this peptide sequence, which is highly conserved in all vertebrate species, appears divergent in both Drosophila and Anopheles...
Clearly, the insect MTP peptide A regions lack the overall hydrophobic or amphipathic character required for interfacial binding (Fig. 8B), perhaps explaining the low vesicle-based transfer activity associated with CG9342, in vitro (Fig. 7).

**DISCUSSION**

As an outgrowth of the *Drosophila* genome project, an EST clone displaying 23% identity with human MTP was identified. A similar EST sequence was also deposited in the *Anopheles gambiae* data base. We explored the function of the *Drosophila* CG9342 gene by expressing it along with two carboxyl-terminally truncated forms of apoB in transfected COS cells. The insect protein promoted the assembly and secretion of epitope tagged forms of human apoB34 and apoB41. Furthermore, apoB34 secreted from cells transfected with either human MTP or CG9342 displayed virtually identical density profiles and relative lipid compositions. This indicates that CG9342 is capable of lipidating apoB peptides to a similar extent as human MTP. Despite these functional similarities, the human and *Drosophila* proteins displayed different susceptibilities to two inhibitors of vertebrate MTP. Furthermore, the *Drosophila* protein displayed low vesicle-based TG transfer activity, possibly due to divergence of a predicted hydrophobic alpha-helical peptide thought critical for efficient lipid acquisition and transfer by vertebrate MTP (45). We conclude, based on these criteria, that CG9342 is an ortholog of vertebrate MTP but may possess only a subset of vertebrate MTP functions.

Although we have not experimentally identified the endogenous substrate for *Drosophila* CG9342, we hypothesize that it likely acts upon apoLp-II/I in insect fat body to produce HDLp (16, 17, 46). ApoLp-II/I, also known as retinoid and fatty acid binding glycoprotein, is a 3351-amino acid protein that is found in its processed form associated with insect lipophorins (47, 48). Although apoLp-II/I is a member of the large lipid transfer protein gene family, which includes vitellogenin, apoB, and MTP (18), its relationship to vertebrate lipoprotein assembly has not been fully appreciated (16). In part, this is because HDLp assembly by apoLp-II/I was thought by some to be an extracellular event and also because an insect ortholog of MTP had not been identified (16, 17, 46). With the discovery of insect MTP orthologs, it has now become clear that vertebrate and invertebrate lipoprotein assembly pathways are indeed related phylogenetically. However, the lipoprotein transport pathways are sufficiently distinct in vertebrates and invertebrates to suggest that the MTP orthologs possess overlapping but not identical functions.

The most critical distinction between vertebrate and insect lipoprotein assembly is the site of precursor particle maturaion. Vertebrate lipid secretion from liver and intestine is achieved almost exclusively via apoB-containing lipoproteins and the secretory pathway (49). Recent data suggest that bulk
triglycerides, which are added to apoB during posttranslational particle enlargement in the ER and Golgi, is trafficked from the cytosol into the lumen of the secretory pathway by a process that requires MTP (23–25, 50, 51). In contrast, apoLp-II/I, the putative substrate for 

Drosophila MTP, is secreted from fat body as a relatively lipid poor HDLp particle (17). However, the subsequent expansion of HDLp to low density lipophorin occurs, not within the secretory pathway, but extracellularly using lipid effluxed from fat body cytosol (16, 46, 52). This process is facilitated by a 670-kDa multisubunit extracellular lipid transfer particle (53). Hence, in insects, extensive trafficking of lipids into the secretory pathway would be counterproductive to the pathway of cytosolic lipid mobilization. Together, these findings raise the possibility that invertebrate MTPs have evolved only those functions required for first step particulate transport but not steps associated with the trafficking of bulk lipid into the secretory pathway, an important requisite for second step expansion of apoB-containing particles into mature VLDL and chylomicrons (23, 25). This may explain the low lipid transfer activity of CG9342 that only TG transfer activity was assayed. It is possible that CG9342 possesses a lipid substrate specificity distinct from that of human MTP (54), perhaps reflecting the predominant role of diglycerides in insect lipid transport pathways (52, 55). Alternatively, it is possible that, during particle initiation, MTP transfers only a few key lipid molecules to its apoprotein substrate as part of a multistep process leading to nascent lipoprotein assembly (56). Hence, even a low rate of transfer of either neutral or polar lipids could, in part, underlie the ability of MTP to convert apolipoproteins into nascent emulsion particles during first step lipoprotein assembly.

The concept that vertebrate MTPs may possess roles beyond their capacity to engage in bulk lipid transfer has been hypothesized for some time (5, 7). Based on the well known capacity of MTP to interact physically with apoB, it has been suggested that MTP may function as a chaperone, facilitating one or more conformational transitions essential for the initial lipid acquisition of apoB within the endoplasmic reticulum. In a related function, it has been suggested that MTP serves as a transient structural subunit of apoB, which completes a vitelligenin-like lipid binding cavity (12, 56). The idea that MTP possesses multiple functions, only some of which require lipid transfer, is also supported by the discovery of a chemical inhibitor of lipoprotein secretion that blocks apoB-MTP interactions but has no effect on lipid transfer by MTP in vitro (41, 57). If vertebrate MTPs do indeed possess distinct functions necessary for first and second step assembly, invertebrate MTPs may become powerful tools for dissecting the structural bases for these multifunctional properties.

Another novel finding with practical implications relates to the differential sensitivity of Drosophila CG9342 to two different MTP inhibitors. When tested against vertebrate MTP, BMS-197636, displays an ~600-fold increased potency relative to BMS-20015 (34). Interestingly, the more potent of these two compounds had no apparent effect on Drosophila CG9342 in an apoB41 secretion assay. It is possible that the same modifications that specified enhanced potency against vertebrate MTP also made the inhibitor more selective. Understanding invertebrate MTP structure and function may facilitate the identification of pharmacologic inhibitors that affect only the first step in apoB assembly without attenuating apoB-independent lipid flux into the secretory pathway. Such classes of inhibitors may display reduced liver toxicity relative to current compounds, all of which were selected based on their ability to inhibit both apoB secretion from hepatoma cells and MTP-mediated lipid transfer, in vitro (58). If human MTP can be selectively inhibited, it is also possible that the reverse may be possible, enabling design of new classes of insecticidal compounds.

It has become clear that apoB is part of a larger gene family that includes insect, nematode, and vertebrate vitellogenins, insect apoLp-II/I, and MTP (18, 48). These proteins are collectively termed “large lipid transfer proteins” reflecting the fact that each are of relatively high molecular mass (~97–500 kDa) and each engage in transport of lipids or other apolar substances (18). Although these proteins are evolutionarily related, the type and amount of lipid each transports are quite distinct as are their sites of action and range of biological functions. We propose that, although all large lipid transfer proteins are related, their mechanisms of lipid acquisition have evolved to better achieve new and disparate functions in lipid transport and metabolism. An understanding of the structure, function, and evolution of each member of this diverse and ancient family of proteins will ultimately help define the complex mechanisms responsible for the assembly and secretion of apoB-containing lipoproteins.

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