Nonacylated Human Transferrin Receptors Are Rapidly Internalized and Mediate Iron Uptake*

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The human transferrin receptor is post-translationally modified by the addition of a fatty acyl moiety. In earlier studies, transient expression in Cos cells of human transferrin receptors in which Cys62 or Cys67 was altered to serine provided evidence that Cys62 is the major acylation site of the receptor (Jing, S., and Trowbridge, I. S. (1987) EMBO J. 6, 327–331). To determine whether acylation of the receptor is required for high efficiency endocytosis and iron uptake, wild type and mutant human transferrin receptors have been stably expressed in chick embryo fibroblasts using a helper-independent retroviral vector. In marked contrast to Cos cells, both Cys62 and Cys67 of the wild type human transferrin receptor were acylated in chick embryo fibroblasts. Moreover, their modification to serine did not abolish palmitate labeling, implying that one or both of these serine residues could serve as alternative lipid attachment sites in these cells. The relative labeling of mutant receptors with palmitate and the susceptibility of their lipid moieties to cleavage by hydroxylamine were consistent with Ser62 but not Ser67 serving as a lipid attachment site. Consequently, to obtain human transferrin receptors lacking covalently bound lipid in the chick embryo fibroblasts, it was necessary to alter Cys62 and Cys67 to alanine. Functional studies indicated that these nonacylated mutant receptors were internalized efficiently and mediated iron uptake from human transferrin at a similar rate to that of wild type receptors. We conclude, therefore, that acylation of the human transferrin receptor is not essential for endocytosis and recycling.

The transferrin receptor (TR) binds the serum iron transport protein, transferrin (Tf), and mediates uptake of iron into the cell by the process of receptor-mediated endocytosis (reviewed in Ref. 1). Iron is a component of a variety of essential enzymes and electron transport carriers, and iron transport is closely coupled to cell proliferation. The human TR is a disulfide-bonded homodimer of two 90-kDa subunits. It has an external domain of 671 amino acids, a transmembrane region of 28 amino acids, and an amino-terminal cytoplasmic domain of 61 amino acids (2, 3). The TR is a member of the class of cell membrane proteins that are post-translationally modified by the covalent attachment of palmitate (4, 5). Treatment of the TR isolated from human cells with hydroxylamine at neutral pH cleaved the lipid moiety from the receptor suggesting it is covalently linked to the receptor by a thioester bond. Subsequent analysis of mutant human TRs transiently expressed in simian Cos cells indicated that, in these cells, the major fatty acid attachment site of the receptor was Cys62, with Cys67 a possible minor site (6). Both Cys62 and Cys67 are located close to or within transmembrane region of the receptor on the cytoplasmic face of the plasma membrane. The lipid attachment sites of other palmitoylated membrane proteins have also been identified as cysteine residues that lie close to the cytoplasmic face of the cell membrane (reviewed in Refs. 7 and 8). Despite the fact that a large number of membrane proteins are known to be palmitoylated, little is known about the functional significance of this post-translational modification (7, 8). We have previously shown that palmitoylation of the human TRs transiently expressed in Cos cells is not necessary for transport to the cell surface (6). However, the functional properties of mutant TRs lacking a lipid moiety could not be analyzed further, because the human receptors were only expressed on a small fraction of the transfected cells and their ability to bind human Tf and mediate iron transport could not be distinguished from that of endogenous simian TRs. We have recently described an experimental system that overcomes these problems in which human TRs are expressed in chick embryo fibroblasts (CEF) using a helper-independent retroviral vector (9). High expression of human TRs can be obtained and, as infectious virus is produced by cells transfected with the retroviral vector containing the human TR cDNA, cultures of CEF in which virtually all the cells express recombinant human TRs can be obtained within 1–2 weeks following transfection. Most importantly, as chick TRs do not bind human Tf, mutant human receptors can be analyzed without a direct contribution of endogenous chick receptors in functional assays.

In the studies reported here, we first expressed mutant human TRs in which Cys62 and Cys67 had been altered to serine residues because such mutant receptors were not detectably acylated in Cos cells (6). However, we found that in CEF, Ser62,67 mutant receptors were still acylated. Consequently, mutant human TRs were expressed in which Cys62 and Cys67 were changed to alanine. Metabolic labeling studies with [3H]palmitate demonstrated that the Ala62,67 mutant receptors were not acylated significantly but nevertheless are internalized efficiently and mediate iron transport normally.

**Experimental Procedures**

Construction of Mutants—FnuDII-XbaI fragments encoding the wild type, Ser62, Ser67, and Ser62,67 mutant TRs, respectively, were

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† The abbreviations used are: TR, transferrin receptor; Tf, transferrin; DMEM, Dulbecco’s modified Eagle’s medium; BSA, bovine serum albumin; PBS, phosphate-buffered saline; SDS, sodium dodecyl sulfate; CEF, chick embryo fibroblasts.
excised from pJTR vectors (6). Their recessed XhoI 3' ends were filled in using the Klenow fragment of Escherichia coli DNA polymerase and then cloned into the Smal site of the adaptor plasmid CLA 12 (10). Clal fragments encoding the mutant and wild type human TRs were then excised and cloned into the retroviral expression vectors RCAS or BH-RCAS (10). For mutagenesis to prepare Ala(62-67) mutant TRs, the Clal fragment encoding the wild type human TR was specially designed to have an XhoI site within it. Oligonucleotide site-directed mutagenesis was performed by the method of Kunkel (11) as described previously (9). The mutations were verified by dyelexonucleotide sequencing of the RCAS constructs using the Sequenex kit (United States Biochemical Corp., Cleveland, OH) according to the manufacturer's directions.

Expression of Mutant Human TRs in CEF—CEF were prepared from fertilized eggs (SPAFAS, Norwich, CT) and grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 1% (v/v) chicken serum, 1% (v/v) defined calf bovine serum (Hyclone, Logan, UT), and 2% (v/v) tryptose phosphate broth (Difco). CEF were transfected with 30 ng of retroviral construct DNA per 10-cm tissue culture plate of ~40% confluent cells using the Polybrene/dimethyl sulfoxide method (12). Cultures were monitored for the expression of human TRs by indirect immunofluorescence staining of cells plated on cover slips with B3/25 monoclonal antibody (9, 13). Virtually all cells expressed human TRs in 2 weeks after transfection and were usually used for experiments within the next 6 weeks. For growth studies, cells were plated at a cell density of 10⁶ cells/cm² in Costar tissue culture plates 24 h prior to the binding assay. Cells were incubated in serum-free DMEM for 1 h at 37 °C and then washed in 0.5 ml of 1 M NaOH and radioactivity counted in a gamma counter. ³⁵Fe uptake by uninfected CEF was ~2% that of cells expressing human TRs. The relative levels of human TRs expressed on the various CEF populations were determined in each experiment. After preincubation for 1 h at 37 °C in serum-free DMEM, triplicate wells of cells were incubated with 4 μg/ml [³²P]labeled Tf on ice for 1 h, then washed three times with 1 ml of ice-cold BSA/PBS, and the radioactivity bound to the cells determined.

RESULTS

Expression and Metabolic Labeling of Mutant Human Transferrin Receptors—Wild type and Ser(62, 67), Ser(67), and Ser(62,67) mutant human TRs were expressed in CEF using the helper-independent retroviral vector RCAS as described under "Experimental Procedures." As preliminary experiments indicated that the Ser(62,67) mutant receptors were acylated, mutant receptors were also constructed in which Cys(62) and Cys(67) were modified to alanine and expressed in CEF. The number and affinity of wild type and mutant human receptors expressed on the surface of infected CEF were determined by quantitative binding studies with [¹²⁵I]-labeled human Tf. The level of surface expression varied from 0.9 × 10⁶ receptors per cell for the Ser(62) mutant to 4.9 × 10⁶ receptors per cell for the Ser(62,67) mutant. Dissociation constants for the wild type and mutant receptors ranged from 3.2 to 6.6 nM. These values are similar to those reported previously for the expression of human TRs in this system (9).

To determine the level of acylation of wild type and mutant receptors, replicate cultures of cells were metabolically labeled with either [³⁵S]methionine or [¹⁴C]palmitate, and human TRs were isolated by immunoprecipitation with monoclonal antibody B3/25 and analyzed by SDS-polyacrylamide gel electrophoresis as described (5). After fluorography of the dried gels of [³⁵S]methionine-labeled TRs, gels were washed twice with 200 ml of dimethyl sulfoxide to remove the 2,5-diphe- noxyazole, treated with 200 ml of 1 M hydroxyamine at pH 6.6 for 2 h as described previously (4), and then reprocessed for fluorography. This procedure was repeated for treatment with hydroxyamine at pH 11. Densitometry scanning of fluorographs was performed using a Quick Quant III scanner (Helena Laboratories, Beaumont, TX). 

Metabolic labeling and Endocytosis of Mutant Human Transferrin—[¹²⁵I]-labeled human transferrin was labeled with [¹²⁵I] to a specific activity of 2-4 μCi/μg using Enzymobeads (Bio-Rad) according to the manufacturer's directions. The number of cell surface TRs and their dissociation constants (Kd) were estimated by Scatchard analysis of [¹²⁵I]-labeled Tf binding at 4 °C. Cells were plated at a density of 5-7 × 10⁵ cells/cm² in 24-well Costar tissue culture plates 24 h prior to the binding assay. Cells were incubated in serum-free DMEM for 1 h at 37 °C and then washed once with ice-cold 0.15 M NaCl, 0.01 M sodium phosphate buffer (pH 7.4) containing 0.1% bovine serum albumin (BSA/PBS). [¹²⁵I]-Labeled Tf (5.0-500 ng) in 0.15 ml of BSA/PBS was added to duplicate wells and incubated at 4 °C for 90 min. Cells were then washed three times with 0.5 ml of ice-cold BSA/PBS, removed from the wells with 0.5 ml of 1 M NaOH, and the radioactivity counted in a gamma counter. Nonspecific binding at each concentration of [¹²⁵I]-labeled Tf determined by addition of a 100-fold excess of unlabeled human Tf was less than 10% of specific binding. Cells in replicate wells were counted in a Coulter counter.

Insights into the endocytosis of mutant and wild type human TRs expressed on CEF were performed as described previously (9). Briefly, to measure the kinetics of internalization, cells were incubated with 4 μg/ml [¹²⁵I]-labeled Tf on ice for 1 h and washed three times with 1 ml of ice-cold BSA/PBS. Prewarmed DMEM (0.5 ml) containing 0.1% BSA and 1 μCi/ml unlabeled human Tf was then added in the same way. After incubation at 37 °C for various times, for the zero time point, the ice-cold medium was added to the wells and remained immediately. After incubation at 37 °C, the medium was transferred to tubes for counting, the cells washed three times with 1.0 ml BSA/PBS, and then incubated twice for 3 min with 0.5 ml of 0.2 M acetic acid, 0.5 M NaOH, and 24 M HCl. After incubation for these periods, the acid wash procedure described for the kinetic experiments was used to distinguish surface-bound and internalized [¹²⁵I]-labeled Tf.

³⁵Fe Uptake Measurements—Human apoTf was labeled with [³⁵Fe] (FeCl, Amersham Corp.) to a specific activity of 5-10 μCi/ml using nitrotriacetate (14). Cells were plated at a density of 5-7 × 10⁵ cells/cm² in 24-well Costar tissue culture plates 24 h prior to the assay. The following day, cells were washed twice in prewarmed serum-free DMEM and then were incubated in serum-free DMEM containing 0.15 μg/ml (w/v) BSA and 4 μg/ml [³⁵Fe]-labeled Tf at 37 °C for various times. After washing, cells from triplicate wells for each time point were removed in 0.5 ml of 1 M NaOH and radioactivity counted in a gamma counter. ³⁵Fe uptake by uninfected CEF was ~2% that of cells expressing human TRs.
Fig. 1. Palmitoylation of wild type and mutant human TRs expressed in CEF. Replicate cultures of CEF expressing wild type or mutant human TRs were metabolically labeled with [35S]methionine and [3H]palmitate as described under "Experimental Procedures." Cell lysates were prepared and human TRs immunoprecipitated from equal cell equivalents using B3/25 monoclonal antibody. Immunoprecipitates were then analyzed by SDS-polyacrylamide gel electrophoresis on 7.5% acrylamide gels. Similar results were obtained in two other experiments including one independent set of infected CEF.

(data not shown). The radioactivity from [3H]palmitate incorporated into the Ala62,67 mutant receptors, which was lower in other experiments (see Fig. 2), is ascribed to metabolic conversion to amino acids.

Hydroxylamine Treatment of [3H]Palmitate-labeled Wild Type and Mutant Human TRs—To investigate the nature of the linkage of the acyl moieties attached to the wild type and mutant receptors, [3H]palmitate-labeled receptors were treated sequentially with 1 M hydroxylamine at pH 6.6 and 11.0. Treatment with hydroxylamine at neutral pH virtually quantitatively removed the lipid moieties of wild type and mutant receptors. However, the [3H]palmitate label was cleaved from both these mutant receptors by hydroxylamine at pH 11.0. These results suggest that the fatty acid linkage of wild type human TRs expressed in CEF is a thioester bond as reported previously for TRs isolated from the human T cell line, RPMI 8402 (4). The lipid moiety of the Ser62,67 mutant receptor is also linked exclusively via a thioester bond as judged by its cleavage with hydroxylamine at pH 6.6. In contrast, the lipid moiety of the Ser62,67 mutant TRs is attached via an ester linkage. The low efficiency with which the Ser62 mutant TRs were labeled precludes a firm conclusion as to the fraction of palmitate attached to Cys62 and Ser67, respectively. These data, together with the observation that the radioactivity incorporated from [3H]palmitate into Ser62 and Ser62,67 mutant TRs is about half that of wild type and Ser67 mutant TRs, indicate that both Cys62 and Cys67 serve as acylation sites; furthermore, serine substituted at position 62 but not position 62 is also acylated in mutant receptors expressed in CEF.

Pulse-Chase Experiments of Metabolically Labeled TRs—Previous studies in the human leukemic cell line, CCRF-CEM, suggested that the acyl moiety of the human TR may turn over more rapidly than can be accounted for by degradation of the receptor. (5) The acyl groups of other palmitoylated proteins have also been found to turn over rapidly (8, 15, 16), and it has been suggested that fatty acylation and deacylation may play a role in protein transport from the Golgi cisternae (17, 18). To re-examine whether there is differential turnover of the lipid moiety of wild type TRs and to compare the rate of turnover of the acyl group linked to the Ser62,67 mutant TR via an ester linkage, pulse-chase experiments of receptors biosynthetically labeled with [3H]palmitate or [35S]methionine were performed. In addition, to investigate whether turnover may be related to receptor recycling, Δ3-59 mutant TRs essentially lacking a cytoplasmic domain that are internalized with ~10% of the efficiency of wild type receptors were studied (9). As shown in Fig. 3, the rate of turnover of the [3H]palmitate incorporated into the wild type human TRs was much too slow for acylation and deacylation to be an obligatory step for the internalization and recycling of the receptor in CEF and was similar to the rate of degradation of the [35S]methionine-labeled receptor protein. The kinetics of turnover of the lipid moieties of the Ser62,67 and Δ3-59 mutant TRs were similar to the wild type receptors. Thus, neither the linkage of the acyl group to the receptor nor the frequency with which the receptors are internalized and recycled had a significant effect on the rate of fatty acid turnover.

Ala62,67 Mutant TRs Are Internalized Efficiently and Mediate Fe Uptake—To investigate whether acylation of the human TR is required for its role in iron uptake, the ability of the
FIG. 3. Pulse-chase experiments of \([^{3}H]\)palmitate- and \([^{35}S]methionine-labeled wild type and mutant receptors. Cells were metabolically labeled with \([^{3}H]\)palmitate and \([^{35}S]methionine for 2 h as described under "Experimental Procedures," washed twice with DMEM, and incubated for various chase periods in DMEM supplemented with 1% (v/v) chicken serum, 1% (v/v) defined calf bovine serum, and 2% (v/v) tryptose phosphate broth. Immunoprecipitates of human TRs were prepared with B3/25 monoclonal antibody and analyzed by SDS-polyacrylamide gel electrophoresis. Exposure of the fluorogram was for 2 days. The data shown are from one of two similar pulse-chase experiments.

FIG. 4. Distribution of cell surface and intracellular wild type and mutant receptors under steady-state conditions. CEF expressing wild type and mutant human TRs were incubated with \(^{125}\)I-labeled human Tf for 1 h at 37 °C as described under "Experimental Procedures." The results shown represent the mean value ± SE. of nine independent experiments.

FIG. 5. Uptake of \(^{59}Fe\) from human Tf by CEF expressing wild type or Ala\(^{62,67}\) mutant human TRs. Uptake of \(^{59}Fe\) and expression of human TRs on the surface of CEF were determined as described under "Experimental Procedures." The figure shows \(^{59}Fe\) uptake expressed on a per surface receptor basis and each point represents the mean value ± S.E. of three independent experiments.

FIG. 6. Growth of CEF expressing wild type and Ala\(^{62,67}\) mutant receptors in tissue culture medium supplemented with human Tf. CEF were plated at 1.5 \(\times 10^4\) cells/cm\(^2\) in tissue culture medium lacking chick serum and supplemented with human Tf as described under "Experimental Procedures." Each point represents the mean of cell counts from triplicate cultures.

and chick TRs do not bind human Tf, the functional status of mutant human receptors can also be assessed by growth assays under conditions in which mammalian Tf is the only source of iron (9). Consistent with the results of the \(^{59}Fe\) uptake studies, CEF expressing Ala\(^{62,67}\) mutant TRs were able to accumulate sufficient iron from human Tf to proliferate normally (Fig. 6).

DISCUSSION

In the studies reported in this paper, we set out to investigate the biological role of acylation of the human TR using an experimental system in which wild type and mutant receptors were expressed at high levels in CEF using a helper-independent retroviral vector (9). Initially, we expressed mutant receptors in which cysteine residues at positions 62 and 67 were altered to serine. Previous studies in Cos cells had indicated that Cys\(^{62}\) was the major acylation site in the human TR with Cys\(^{67}\) a possible minor site and that substitution of serine for cysteine abolished acylation. We found that this was not the case when the Ser\(^{62,67}\) mutant human TRs were expressed in CEF. The mutant receptors were still acylated and hydroxylamine treatment of the \([^{3}H]\)palmitate-labeled receptors strongly suggested that the fatty acid moiety was linked via an ester bond. Analysis of single mutants in which cysteine residues at positions 62 and 67 were independently replaced by serines is consistent with Ser\(^{67}\) being the major ester-linked lipid attachment site. The ability of a serine residue substituted for a cysteine to serve as an alternative acylation site in membrane-associated proteins has not been
documented previously. Three well-characterized examples of acylated proteins, the vesicular stomatitis virus G protein, p21HCMV, the transforming protein of the Kirsten sarcoma virus, and the human β-adrenergic receptor, are normally palmitoylated on cysteine residues. Alteration of these residues, Cys406 in the viral G protein (19), Cys180 and Cys284 in p21HCMV (20), and Cys241 in the human β-adrenergic receptor (21), to serine abolishes palmitoylation when the mutant proteins are expressed in Chinese hamster ovary cells. However, this probably does not reflect an intrinsic structural difference between these proteins and the human TR because the receptor itself is not acylated on serine in Cos cells (6). A more likely explanation is that there is a palmitoyl acyltransferase activity in CEF capable of transferring an acyl group to serine that is not present in Cos cells or Chinese hamster ovary cells. Whether this represents a protein O-acyltransferase distinct from the acyltransferase that mediates the palmitoylation of cysteine remains to be determined. The primary structural requirements for palmitoylation of proteins are not known. However, during studies of the role of the TR cytoplasmic domain we expressed a mutant receptor lacking residues 3–59 of the 61-amino acid cytoplasmic tail in CEF. This mutant receptor is acylated as efficiently as the wild type molecule, indicating that residues amino-terminal to Lys60 are not required for addition of palmitate to the receptor (Fig. 3).

Because Ser57 of mutant human TRs can serve as an acylation site in CEF, we constructed the Ala62,67 mutant receptor in order to evaluate the role of acylation in receptor function. In all major respects, the mutant receptors were indistinguishable from wild type receptors. The Ala62,67 mutant receptors bind human Tf and were internalized efficiently, and their ability to mediate iron uptake was not significantly impaired. Thus, acylation does not appear to be required for functional human TRs. Nevertheless, this does not preclude the possibility that acylation of the receptor may have a more subtle influence on receptor internalization and recycling than could be detected by the assays we employed or that it influences other properties of the receptor. In the latter, however, we did not detect any difference in the rate of degradation of wild type, Ala62,67, or Ser62,67 mutant receptors biosynthetically labeled with [35S]methionine (Fig. 3).

The effect of palmitoylation on the biological properties of other membrane-associated proteins has not been extensively investigated. It was originally thought that palmitoylation of p21HCMV on Cys186 was required for association of the protein with the inner surface of the plasma membrane and for transforming activity. It is now known, however, that this cysteine residue is modified by the addition of a polyisoprenoid, farnesol, and that some ras proteins are not palmitoylated but still bind, albeit less tightly, to the plasma membrane and induce transformation (20, 22). More recently, it has been reported that mutation of Cys241 in the carboxyl tail of the human β-adrenergic receptor exhibits a drastically reduced ability to mediate isoproterenol stimulation of adenyl cyclase although the molecular basis of the functional impairment is unknown (21). However, the functional significance of the lipid moieties of most acylated proteins remains unknown.

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S Q Jing and I S Trowbridge

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