Expression Cloning of Human Globoside Synthase cDNAs

IDENTIFICATION OF β3Gal-T3 AS UDP-N-ACETYLGLUCOSAMINE:GLOBOTRIAOSYLGLYCERAMIDE β1,3-N-ACETYLGLUCOSAMINYLTRANSFERASE∗

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By using a eukaryotic cell expression cloning system, we have isolated cDNAs of the globoside synthase (β1,3,4-galactosylgalactosaminyltransferase) gene. Mouse fibroblast L cells transfected with SV40 large T antigen and previously cloned Gb3/CD77 synthase cDNAs were co-transfected with a cDNA library prepared from mRNA from human kidney together with Forssman synthase cDNA, and Forssman antigen-positive cells were screened using an anti-Forssman monoclonal antibody. The isolated cDNAs contained a single open reading frame predicting a type II membrane protein with 351 amino acids. Surprisingly, the cDNA clones turned out to be identical with previously reported β3Gal-T3, which had been cloned by sequence homology with other galactosyltransferases. Substrate specificity analysis with extracts from cDNA-transfected L cells confirmed that the gene product was actually β1,3,4-galactosylgalactosaminyltransferase that specifically catalyzes the transfer of N-acetylglucosamine onto globotriaosylglyceramide. Results of TLC immunostaining of neutral glycolipids from the cDNA-transfected cells also supported the identity of the newly synthesized component as globoside. The results show that glycosyltransferases apparently belonging to a single glycosyltransferase family do not necessarily catalyze reactions utilizing the same acceptor or even the same sugar donor. The globoside synthase gene was expressed in many tissues, such as heart, brain, testis, etc. We propose the designation β3GalNAc-T1 for the cloned globoside synthase gene.

Glycosphingolipids are synthesized by the sequential action of glycosyltransferases starting from the glucosylation of ceramide (1). β1,4-Galactosyltransferase then synthesizes lactosylceramide (LacCer),1 which is a common precursor structure of the majority of glycosphingolipids present in mammals and birds. Three major series of glycolipids are synthesized starting from LacCer by addition of β1,3-N-acetylglucosamine (lacto/neolacto-series), α2,3-sialic acid (ganglio-series), or α1,4-galactose (globo-series). Moreover, addition of N-acetylgalactosamine in a β1,4-linkage leads to the synthesis of asialo-ganglio series.

Globo-series glycolipids are ubiquitously present in human and many other mammalian tissues, whereas some tissues such as kidney, placenta, testis, erythroid cells, heart, and spleen express them at high levels. Recently, the key enzyme to initiate the synthesis of the globo-series glycolipid, Gb3/CD77 synthase (α1,4-galactosyltransferase, α1,4Gal-T), gene has been cloned by us (2) and other groups (3, 4). The expression pattern of the gene also indicated that globo-series glycolipids may be more widely expressed than previously believed, suggesting the importance of structures containing the globo-series backbone.

Globoside is the most prominent neutral glycosphingolipid in human erythrocytes (5) and is an essential structure of blood group P antigen (6). Globoside is synthesized from globotriaosylglyceramide (Gb3, Pα antigen) by the action of β1,3-N-acetylgalactosaminyltransferase (β1,3GalNAc-T). Therefore, Pα individuals lack β1,3GalNAc-T activity and accumulate the precursor Pα. On the other hand, Pβ individuals lack Gb3/CD77 synthase activity with essentially intact β1,3GalNAc-T activity (7), and they lack the expression of both Gb3/CD77 and globoside.

Recently, a large number of glycosyltransferase genes responsible for the synthesis of glycoproteins and glycolipids have been isolated. Many of them could be classified into several families based on their similarities in primary structures, e.g. there have been 9 fucosyltransferase genes (8), 18 members of sialyltransferase genes (9), 7 β4-galactosyltransferase genes (10), 5 β3-galactosyltransferase genes (11), and 7 peptide N-acetylgalactosaminyltransferase genes (12) isolated to date. However, no glycosyltransferases responsible for β1,3GalNAc linkages have been isolated so far.

In this study, we have isolated cDNAs of β1,3GalNAc-T responsible for the synthesis of globoside using a eukaryotic cell expression cloning system and taking advantage of the

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Previously clonedGb3/CD77 synthase. To our surprise, the cloned cDNAs of globoside synthase turned out to be identical with β1,3Gal-T3 which was considered to be a galactosyltransferase responsible for the formation of Galβ1,3GlCNac-R structures, although no enzymatic activity was reported for the expressed cDNA (11). These results suggest that glycosyltransferases that seem to be members of a transferase family do not necessarily catalyze enzyme reactions with either the same sugar donor or the same acceptor structure. We propose here the name β3GalNAc-T1 for the cloned globoside synthase gene.

EXPERIMENTAL PROCEDURES

Materials—UDP-GalNAc, LacCer, globotriaosylceramide (Gb3), and globoside (Gb4) were purchased from Sigma. GM3 and GD3 were purchased from Snow Brand Milk Products Co. (Tokyo, Japan). UDP-[3H]GalNAc was obtained from New England Nuclear. Culture supernatant of anti-Forsmann glycolipid monoclonal antibody (mAb) M1/22.25.8.HL was prepared from a hybridoma line obtained from American Type Culture Collection. pBS-SV-RT, an expression vector for SV40 large T antigen, was obtained from the Japanese Cancer Research Resources Bank (Tsukuba, Japan). An expression vector of Forsmann antigen synthase (12) was constructed by inserting HindIII/HindIII digested fragment from pBS-35 (14) into pCDM8. An expression vector of Gb3 synthase pCDNA1.1/VTI-1 was prepared by inserting Xhol fragment from pVTI-1 (2) into the XhoI site of pCDNA3.1 (Invitrogen).

Cell Lines—A mouse fibroblast L cell was kindly provided by Dr. A. P. Albino (Sloan-Kettering Cancer Center, New York) and was maintained in Dulbecco’s modified Eagle’s minimal essential medium containing 7.5% fetal bovine serum. A mouse fibroblast line, designated 1B9, used as a recipient cell in the transient expression system was prepared by co-transfection of L cell with pBS-SV-RT (SV40 large T Ag) and pCDNA1.1/VTI-1 (2). 1B9 was established from neo-resistant transfected L cells by screening the expression of Gb3 and SV40 large T Ag using anti-Gb3 mAb 38.13 (15) and mouse anti-SV40 large T Ag mAbs Pab101 (Santa Cruz Biotechnology, Inc.), respectively. The expression of SV40 large T Ag and Gb3 was detected by an indirect immunofluorescence assay and flow cytometry, respectively. Stable transfected cells were maintained in Dulbecco’s modified Eagle’s minimal essential medium containing 7.5% fetal bovine serum and G418 (300 μg/ml).

Expression Cloning of Human Globoside Synthase cDNA—Plasmids of the human adult kidney cDNA library (Invitrogen) were transfected into 1B9 cells together with pCDM8/FS using DEAE-dextran as described (16). After 48 h, the transfected cells were detached by trypsinization and incubated with a rat mAb M1/22.25.8.HL on ice for 1 h. After washing, cells were plated on dishes coated with goat anti-rat IgM (ICN) as described (17). Plasmid DNA was rescued from the panned cells by preparing Hirt extracts and transformed into Escherichia coli XL-1 Blue (Stratagene). The same procedure was repeated four times. By using microscale transfection and immunofluorescence assays, cDNA clones that determined the Forsmann glycolipid expression were isolated.

Sequencing Analysis—The nucleotide sequence of the cloned cDNAs was determined by dideoxynucleotide termination sequencing using the PRISM dye terminator cycle sequencing kit and a model 310 DNA sequencer (Applied Biosystems). Amino acid sequence and hydropathy analyses were performed with Genetyx-Mac software, version 8.0 (Software Development, Tokyo). Genomic organization was determined by comparison between the cDNA sequence and the genomic one from the Human Genome Project.

Preparation of the Membrane Fraction—L cells at 80% confluency were transfected with expression vectors using the DEAE-dextran method. After 80 h, the cells were collected and lysed in ice-cold phosphate-buffered saline containing 1 mM phenylmethylsulfonyl fluoride using a nitrogen cavitation apparatus as described previously (18). Nuclei were removed by low speed centrifugation, and the supernatant was centrifuged at 100,000 × g for 1 h at 4 °C. The pellet was resuspended in ice-cold 100 mM MES buffer (pH 6.5) and used as an enzyme source.

Enzyme Assay—The N-acetylgalactosaminytransferase assay was performed in a mixture containing 10 mM MnCl2, 0.3% Triton X-100, 100 mM MES buffer (pH 6.5), 0.1 mM UDP-[3H]GalNAc (160,000 cpm/pmol), 200 μM of the membrane extracts, and 20 μg of substrates in a total volume of 50 μL. After incubating at 37 °C for 3 h, the reaction was terminated by the addition of 0.5 ml of water. The products were isolated with a C18 Sep-Pak cartridge (Waters, Milford, MA).
pCDNA3.1/VTR-1, together with pBS-SVT containing SV40 large T antigen for extrachromosomal replication of the transfected plasmids. A transfectant line designated 1B9 contained abundant Gb3 and a negligible level of Gb4 and Forssman antigen (data not shown). Moreover, the nuclei of 1B9 line were strongly stained by anti-SV40 large T antigen antibody under fluorescence microscopy (data not shown). Thus, we could expect the expression of Forssman antigen after transfection of pCDM8/FS and Gb4 synthase cDNA which should have been contained in the human kidney cDNA library (Fig. 1, A and B). Because the extracted plasmids from panned cells were amplified in E. coli XL-1 Blue in the presence of ampicillin, only the plasmids from the library could be rescued.

Isolation of cDNA Clones of Globoside Synthase Gene—Following four rounds of enrichment by transfection of the cDNA library, panning with anti-Forssman mAb M1/22.25.8.HL, and rescue of plasmids by Hirt extraction, a pool of approximately 1000 bacterial colonies was identified to be positive in microscale immunofluorescence assays. These colonies were subdivided until three independent clones were identified to direct the expression of Forssman antigen when cotransfected with Forssman synthase cDNA into the 1B9 cell. Consequently, two clones of putative globoside synthase gene (designated type 1 and 2) with different 5'-untranslated regions were identified (Fig. 2). These two clones contained alternatively spliced transcripts, i.e. type 1 transcript contained a single exon and type 2 consisted of five exons (Fig. 2 B). All intron sequences at the exon-intron junctions conform to the GT-AG consensus (data not shown). Since the nucleotide sequence of the open reading frame was essentially same, type 1 clone was selected for further analysis and named b1,3GalNAc-T-1. As shown in Fig. 1 C, only 1B9 cells cotransfected with b1,3GalNAc-T-1 and Forssman synthase gene expressed a definite amount of Forssman antigen, whereas those transfected with either b1,3GalNAcT-1 or Forssman synthase gene plasmids did not. These data indicated that b1,3GalNAc-T-1 is responsible for the expression of globoside.

Amino Acid Sequence Analysis of b1,3GalNAc-T-1—The open reading frame predicted a protein of 331 amino acids in length with a calculated molecular mass of 39,511. Unexpectedly, when this amino acids sequence was compared with other cDNAs in the database, it was found to be identical to human b3GalT-3 reported by Amado et al. (11, 34). Although human b3GalT-3 was believed to belong to b3GalT gene family, no galactosyltransferase activity was reported. b1,3GalNAc-T-1 contained five potential N-linked glycosylation sites. The posi-
tion of the AUG start codon was determined according to the Kozak consensus sequence (22). Hydropathy analysis (23) indicated one prominent hydrophobic segment of 23 residues in length in the amino-terminal region, predicting that the protein had the type II transmembrane topology characteristic of many other glycosyltransferases cloned to date.

A comparison between the β1,3GalNAc-T-1 isolated here and the previously characterized β3GalTs proteins revealed that various sequence motifs in the putative catalytic domains were conserved (Fig. 3). In contrast to β3GnT, the four conserved cysteine residues that are considered to be essential for maintenance of the tertiary structures of β3GalTs are aligned with those of β1,3GalNAc-T-1 gene (Fig. 3).

N-Acetylgalactosaminyltransferase Activity of β1,3GalNAc-T-1—To confirm the N-acetylgalactosaminyltransferase activity of β1,3GalNAc-T-1, L cells were transiently transfected with control pCDNA3.1 vector or pCDNA3.1/β1,3GalNAc-T-1, and the membrane extracts were assayed for N-acetylgalactosaminyltransferase activity using UDP-[3H]GalNAc as a donor. The enzyme catalyzed the addition of [3H]GalNAc efficiently onto Gb3 (79 pmol/h/mg of protein) resulting in the synthesis of a new component with the same migration as standard Gb4, whereas LacCer, GM3, GD3, and Gb4 were not utilized as an acceptor (Fig. 4B), indicating that this enzyme is different from GA2/GM2/GD2 synthase or Forssman glycolipid synthase. No activity was detected in the extracts prepared from mock-transfected cells (Fig. 4A).

Synthesis of Gb4 in the Transfectant Cells—To investigate the expression of Gb4 by β1,3GalNAc-T-1 in vivo, glycolipids were extracted from 1B9 cells transfected with pCDNA3.1 or pCDNA3.1/β1,3GalNAc-T-1 and then separated on TLC. As shown in Fig. 5A, 1B9 cells transfected with pCDNA3.1/β1,3GalNAc-T-1 showed definite Gb4 bands in TLC, whereas the transfectant cells with pCDNA3.1 alone showed no Gb4 band. In order to confirm the neo-synthesis of Gb4, TLC-immunostaining was conducted using a human anti-P mAb2 prepared from lymphoid cells from an individual with p phenotype. As shown in Fig. 5B, the glycosphingolipids extracted from the transfecant cells with β1,3GalNAc-T-1 clearly gave bands like the control Gb4 at the same migration site. None of the other neutral glycolipids were stained, confirming the specificity of the mAb. Thus, the product was confirmed to be Gb4.

Expression of the β1,3GalNAc-T-1 Gene—To determine the expression pattern of the β1,3GalNAc-T-1 mRNA, Northern blotting was performed. Among 12 tissues examined, strong gene expression was observed in brain and heart as reported previously, and moderate expression was detected in lung, placenta, and testis, and low level expression was observed in kidney, liver, spleen, and stomach (Fig. 6).

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DISCUSSION

Globoside was defined as a major sugar-containing lipid of human blood stroma that formed perfectly round globules (spherocrystals) as viewed under microscope, and its name was chosen to reflect its property (24). The main glycolipid structure from hog erythrocyte stroma was also determined to be β-N-acetylgalactosaminyl-(1→3)-galactosyl-(1→4)-galactosyl-(1→4)-glucosyl- ceramide, namely globoside (25). The synthetic pathway of globoside has been recognized in the studies of rare genetic disorders (31). Their molecular mass or to a difference in species studied.

Recently, a function of globoside as an initiator of signal transduction through AP1 and CREB associated with cell adhesion was reported (42). Although globoside has been considered to be an adhesion molecule on epithelial cells to various glycosylation modifications that would increase the predicted molecular mass or to a difference in species studied.

The goal of this study was to isolate β3GalNAc-T cDNA responsible for the synthesis of globoside from Gb3. Surprisingly, the cloned cDNA insert contained a primary structure similar to those of β3Gal-T gene family (β3Gal-T family) and was identical to β3Gal-T3 (11). This β3Gal-T family now consists of 5 published members and several additional ones that have not yet been defined (34). Although β3Gal-T1, β3Gal-T2 (11, 35), β3Gal-T3 (11), and β3Gal-T5 (36, 37) have all been reported to catalyze the transfer of β3-galactosyl onto GlcNAcβ1,3-R residue, expressed human β3Gal-T3 showed no activity (11), and mouse β3Gal-T2 and β3Gal-T3 exhibited only 3–4% of the activity compared with that of mouse β3Gal-T1 (38). β3Gal-T4 was shown to be GM1/GD1b/GalNAcβ1,4-R synthase, i.e., the β3-lactosyltransferase responsible for GalNAcβ1,4-R (39). These findings suggest that the β3Gal-T family is heterogeneous and contains glycosyltransferases that utilize a variety of sugar donors or acceptors. Our results also indicated that authors (11, 38) of the previous studies failed to determine the exact substrate specificity of the so-called “β3Gal-T3” and how EST approach is misleading and how the authors of the previous two papers (11, 38) incorrectly interpreted the results.

Zhou et al. (37) found that β3Gal-T5, which was reported to be involved in the synthesis of sialyl-Lewis, an antigen in gastrointestinal and pancreatic epithelia and tumor cells derived therefrom, was a stage-specific embryonic antigen-3 (SSEA-3) synthase (i.e., a β3,3-galactosylgloboside synthase) (40). Although they did not exclude the existence of other β3Gal-T which could be responsible for the formation of SSEA-3, it seems clear that a member of β3Gal-T family certainly shows dual activity toward GlcNAc and GalNAc-based acceptors (40). Furthermore, Zhou et al. (41) cloned a β1,3-N-acetylgalactosaminyltransferase (β3Gn-T) capable of both initiating and elongating poly-N-acetyllactosamine chains based on the sequence similarity with mouse β3Gal-T1–3. This cDNA product exhibited inverted donor and acceptor specificities (β1,3GlcNAc-transfer onto Galβ1,4-R), whereas it shared the conserved sequence motifs among β3Gal-Ts except for the major of conserved cysteine residues. Together with our results, these data indicate that the β3Gal-T family contains diverse glycosyltransferases that use various nucleotide sugars and acceptors, and this family might represent enzymes responsible for the catalysis of glycosidic β3,3-linkages.

FIG. 5. TLC analysis of glycosphingolipids isolated from transfected cells. Glycolipids were extracted from 240 μl of IB9 cells transfected with pCDNA3.1 or pCDNA3.1/β3GalNAc-T-1 as described under “Experimental Procedures” and then separated on TLC. A, orcinol (left) or primulin spray (right) was performed to detect the bands. Lane 1, neutral glycolipids extracted from human B red blood cells; lane 2, Gb4 (2 μg); lanes 3 and 5, extracts from IB9 transfected with pCDNA3.1 alone (derived from 50 μl of cells); lanes 4 and 6, extracts from IB9 transfected with pCDNA3.1/β3GalNAc-T-1 (50 μl of cells). B, TLC immunostaining of globoside. TLC was prepared as in A, and glycolipids were blotted and then stained by mAb 9H6 as described under “Experimental Procedures.” Lane 1, neutral glycolipids extracted from human B red blood cells; lane 2, Gb4 (0.5 μg); lane 3, LacCer (0.5 μg); lane 4, Gb3 (0.5 μg); lane 5, extracts from IB9 transfected cells with pCDNA3.1 alone (derived from 5 μl of cells); lane 6, extracts from IB9 transfected with pCDNA3.1/β3GalNAc-T-1 (5 μl of cells).

FIG. 6. Expression pattern of the β1,3GalNAc-T-1 gene in various human tissues. Northern blots with 2 μg of poly(A)+ RNA from 12 adult human tissues were probed with 32P-labeled β1,3GalNAc-T-1 cDNA as described under “Experimental Procedures.” The same filters were probed with the β-actin cDNA after removing the radioactivity. The sizes of the markers are indicated at the left, and those of bands are at the right.
bacteria such as uropathogenic E. coli (43), and a receptor for pig edema disease toxin (44–46), its physiological function in vivo has never been elucidated. If signals transduced via globoside regulate transcription factors like API and CREB, the control of the gene expression of globoside synthase would be very critical in the development and differentiation, and the availability of globoside synthase gene would strongly promote researches in these fields.

Acknowledgment—We thank Dr. K. O. Lloyd at Memorial Sloan-Kettering Cancer Center for carefully reading the manuscript.

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J. Biol. Chem. 2000, 275:40498-40503.
doi: 10.1074/jbc.M006902200 originally published online September 18, 2000

Access the most updated version of this article at doi: 10.1074/jbc.M006902200

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