An Alternatively Processed mRNA Specific for γ-Glutamyl Transpeptidase in Human Tissues*

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Human γ-glutamyl transpeptidase (GGT* has been described before (20). Two DNA fragments generated in an indirect fashion were used to screen this library. Four oligonucleotides based on the published rat GGT cDNA sequence (14) were synthesized from a single mRNA encoding a 64-kDa peptide (4, 5). GGT is mainly distributed in tissues exhibiting absorptive and secretory processes (1). The highest activity is found in kidney and intestinal cells (1-3). In normal adult liver, the GGT activity is low and mainly located in bile ducts and canicular membranes of the hepatocytes (6). In this organ, increases in activity are observed under various physiological and pathological conditions (7, 8). Several experiments have demonstrated that these increases are often associated with structural changes in the sugar chains of the enzyme, as evidenced by a variation in the pattern of GGT isoforms in serum (9, 10). Antibodies, specific for GGT isoforms from a human primary hepatoma, have been shown to be useful for the diagnosis of some neoplastic diseases (11). In human serum (12) or in rat liver (13) such antibodies recognize reactive species which are not directly correlated with GGT activity, suggesting the presence of altered forms of GGT.

Recently we have cloned the cDNA encoding the rat kidney GGT (14), and using this cDNA we have demonstrated that several genes or pseudogenes are present in the human genome (15) on chromosome 22 (16). According to the recent cloning of GGT mRNA from human placenta (17), fetal liver (18), or the human hepatoma cell line Hep G2 (19), this multigene family codes for the same GGT precursor.

In the present report we describe the isolation and sequence of two cDNAs from human adult and fetal liver libraries. These cDNAs have a 22-bp insertion as compared with other known sequences (17-19). This insertion, apparently generated by alternative splicing, induces a frameshift resulting in an open reading frame that could code for an altered GGT.

EXPERIMENTAL PROCEDURES

Materials

Escherichia coli DNA polymerase I and Klenow fragment were obtained from New England Biolabs. Restriction endonucleases were purchased from New England Biolabs, Boehringer Mannheim, or Genofit S.A. TaqI polymerase was obtained from Stratagene. Radio-labeled nucleotides, cDNA synthesis kit, human placental ribonuclease inhibitor, and nylon membrane (Hybond N) were from Amersham Radiochemical Centre. All the other reagents were of analytical grade (Sigma, Merck, or BDH). The human genomic library has been already described (15).

Methods

Construction and Screening of the Human Fetal Liver cDNA Library—The construction of the flg11 human fetal liver cDNA library has been described before (20). Two DNA fragments generated in an indirect fashion were used to screen this library. Four oligonucleotides based on the published rat GGT cDNA sequence (14) were synthesized. They consisted of nucleotides 384-420, 1334-1363, 1464-1505, and 1817-1849, respectively, of the rat cDNA sequence. All four

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBankTM/EMBL Data Bank with accession number(s) J00222.

The abbreviations used are: GGT, γ-glutamyl transpeptidase; SDS, sodium dodecyl sulfate; bp, base pairs.
oligonucleotides were kinased and used to screen a rat kidney cDNA library obtained from Clontech. One clone to which both probes hybridized was partially sequenced and shown to be highly homologous to the rat GGT cDNA sequence. This clone in turn was subcloned into the pUC19 vector, digested with EcoRI, and sequenced as described previously (22).

The adult human liver cDNA library was constructed in the gtl1 vector described by Young and Davis (23). Double-stranded cDNA was prepared in the presence of reverse transcriptase, ribonuclease H, and DNA polymerase, according to Amersham procedures. After methylation of the cDNA with EcoRI methylase, addition of EcoRI linkers, digestion with EcoRI, and size fractionation on a Bio-Gel A-50m column, the cDNA fragments were inserted in the EcoRI site of the gtl1 vector (2 μg). After in vitro packaging, 530,000 independent clones were obtained of which 95% were recombinant.

Approximately 3 × 10^6 clones were screened according to the method of Benton and Davis (24) using the 1.6-kilobase-long insert from the rat kidney cDNA clone Psp64/39-1 as a probe (16). The probe was purified by electrophoresis on agarose gel and radioabeled by nick translation to a specific activity of 5 × 10^9 cpm/μg. Filters were prehybridized in 6 SSC (1 SSC = 0.15 M NaCl, 15 mM sodium citrate), 1 × Denhardt's, 0.1% SDS, 0.2 g/liter bovine serum albumin (fraction V) containing 100 μg/ml of denatured salmon sperm DNA for 5 h at 68 °C; the hybridization was performed overnight at 68 °C in 2 SSC, 1 × Denhardt's, 0.01% SDS, 5 mM NaCl, 0.1% ribonuclease H, and DNA polymerase, according to Amersham procedures. After methylation of the cDNA with EcoRI methylase, addition of EcoRI linkers, digestion with EcoRI, and size fractionation on a Bio-Gel A-50m column, the cDNA fragments were inserted in the EcoRI site of the gtl1 vector (2 μg). After in vitro packaging, 530,000 independent clones were obtained of which 95% were recombinant.

During hepatectomy, 2 g of tissue were immediately frozen in liquid nitrogen and stored at −80 °C until the preparation of the RNA. This was done essentially by the method described by Chirgwin et al. (21). Poly(A)* RNA was isolated using oligo(dT)-cellulose chromatography as described previously (22).

RESULTS

Cloning of the Human Fetal Liver cDNA Specific for GGT—Only two positive clones were obtained after screening 6.3 × 10^6 clones from the human fetal liver cDNA library as described under "Methods." The longer of the two clones is 2632 bp exclusive of a short run of A residues at the 3′-end (Fig. 1). There is a 743-bp-long 5′-untranslated region in front of one open reading frame of 366 amino acids. A second open reading frame is observed beginning at position 1055 and could encode a protein of 225 amino acids encompassing the complete sequence of the small GGT subunit. In the 3′-noncoding region (160 bp) the polyadenylation signal is found 43 bp upstream from the poly(A) tail.

Cloning of the Human Adult Liver cDNA Specific for GGT—In screening the human adult liver cDNA library using a rat cDNA probe specific for GGT, only one positive clone out of 3 × 10^6 was identified. This clone has an insert of 963 bp. In this sequence, the first 794 bp correspond to the 3′-region of the coding sequence (Fig. 1). They are followed by a 169-bp 3′-untranslated region, and a polyadenylation signal AA-TAAA is found 52 bp upstream of the poly(A) tail (Fig. 2). There is a complete homology between this GGT cDNA isolated from human adult liver and the 3′-part of the human fetal liver cDNA. The 3′-untranslated region is 9 bases longer in the adult liver cDNA than in the fetal liver cDNA.

Comparison with Other Known Human cDNA Sequences Specific for GGT—The sequences, for the two cDNAs we obtained, were compared with sequences coding for GGT isolated from human placenta (17), human fetal liver (18), and Hep G2 hepatoma cells (19) (Fig. 2). The 5′-noncoding sequences are organized differently. They are identical from +1 to −88 except for single base pair differences at positions −23 and −84 in the Hep G2 cDNA relative to the other sequences. A region from −89 to −243 in the human fetal liver cDNA (present study) is observed in the Hep G2 cDNA from position −207 to −361. At position −139 in our clone, during the purification in order to assess the contamination of the microsomes by the supernatant.

RNA Amplification by Polymerase Chain Reaction Using Taq Polymerase—Poly(A)* RNAs were prepared from human adult kidney, placenta, brain, liver, human fetal liver and kidney, and Hep G2 cells as described for the adult liver cDNA library, with two cycles of oligo-dT columns at the end.

Amplification of the mRNA sequences was done according to Simpson et al. (29) with minor modifications. The synthesis of the first cDNA strand was done according to the Amersham cDNA synthesis system using 1–5 μg of poly(A)* mRNA or 5 μl of the polysomal samples, oligo-dT as primer, and reverse transcriptase. For the polymerase chain reaction amplification, 20% of the first strand cDNA was amplified with Taq1 DNA polymerase in 10 mM Tris-HCl, pH 8.3, 50 mM KCl, 3 mM MgCl2, 0.01% gelatin containing 200 μM of each deoxynucleotide and 70–100 ng of the two synthetic oligonucleotide primers. After the addition of 2 units of Taq1 DNA polymerase, the solution was mixed and covered with mineral oil. The DNA was heat-denatured at 94 °C (1 min) and allowed to cool at 55 °C (1 min) for primer hybridization. Synthesis was then performed at 72 °C (1.5 min). 30 and 60 runs of denaturation, hybridization, and synthesis were performed on mRNA isolated from tissues or polysomes, respectively. After the amplification reaction, 20% of the samples were loaded on a 3% agarose low melting gel in TBE buffer (0.089 M Tris, 0.089 M boric acid, 0.02 M EDTA). The DNAs were then transferred onto a Hybond N membrane. The membrane was prehybridized and then hybridized overnight at 37 °C in 6 X SSC, 5 × Denhardt's, 0.1% SDS, 5 mM EDTA containing 100 μg/ml denatured salmon sperm DNA. 100 ng of 5′-end-labeled synthetic oligonucleotides (≈5 × 10^7 cpm/50 ml) were used as probes.

The blots were washed 3 times for 1 h at 53 °C in 1 liter of 6 X SSC, 0.1% SDS and autoradiographed overnight at −80 °C on Amersham hyperfilm MP using two intensifying screens. All oligonucleotides used were synthesized as for DNA sequencing.
An Alternative mRNA for Human GGT Sequences

FIG. 1. Sequence of the human adult and fetal liver cDNA specific for GGT. The adult liver cDNA starts at base 936 (arrow) and is exactly homologous to the human fetal liver sequence except for nine additional bases at the 3'-end of this sequence which are shown in Fig. 2. The 22-bp insertion is underlined and the changes in protein sequence, as compared with other human cDNA sequences (17-19), are boxed. The protein sequences, corresponding to both open reading frames, are represented above and below the nucleic acid sequence. The vertical bar represents the probable NH2-terminal part of the small GGT subunit (33).
An Alternative mRNA for Human GGT Sequences

1) The codon for the entry of the edit codon. 2. sequence in the coding region of the cDNA clones specific for GGT. 1. analysis of the 5'-untranslated regions exist between Hep G2 cDNA and placenta cDNA far analyzed. It should be noted that some other homologous to -253. However, no other homologies were detected between position. A part of this sequence -174 to -243 from human fetal liver is found in the human placenta sequence at -185.

2) The coding sequences of all the clones so far analyzed are identical except for two differences. The first difference is minor; a T instead of a C is found at position 815 in our fetal liver cDNA clone changing in alanine codon to a valine codon. The second difference, and by far more important, is a 22-bp insertion in both our fetal and adult liver cDNAs.

3) The 3'-untranslated region starts at the same position for all the cDNAs. The main difference is a microheterogeneity in the length of the sequence preceding the poly(A) tail. There are three nucleotide differences between placenta cDNA specific for GGT and the other sequences. Since the insertion of 22 bp in the coding sequence necessarily alters the product of this mRNA, we further focused our work on this additional sequence.

Analysis of the 22-bp Insertion at the Gene Level—Four genomic clones corresponding to the different subclasses of human GGT genes (15) were digested by BamHI and hybridized with a labeled oligonucleotide corresponding to the 22-bp insertion found in fetal and adult liver cDNAs. The result of the Southern blot is shown in Fig. 3. Only the clones corresponding to the subclass F15 and F30 hybridized with this oligonucleotide. The faint band on clone F19 disappeared at slightly higher stringency (data not shown).

The human liver cDNA sequences were compared with the sequence of one of these genomic clones (F15) (Fig. 4). This analysis revealed that in the gene the 22-bp domain is located at the 3'-part of an intron. This sequence is bordered at each end by a 3'-acceptor consensus sequence necessary for a correct splicing (30). Therefore, the cDNAs that we characterized reflect the fact that, during maturation of the corresponding mRNAs, the internal 3'-acceptor site was used.

Detection of the 22-Base Insertion in Polysomal RNA from Hep G2 Cells and mRNA from Human Tissues—Using the oligonucleotides corresponding to the 22-bp insertion and to the control sequence as probe, we were unable to detect any GGT-specific sequence in the human liver mRNAs tested by Northern blot analysis. In order to increase the chances of detecting mRNAs containing the 22-base insertion, we used the polymerase chain reaction technique. Two oligonucleotides, designated oligo-A and oligo-B, were selected as described in Fig. 6A and used as primers for the amplification procedure. Amplified products using RNAs from Hep G2 polysomes and supernatant as starting materials were subjected to Southern blot analysis using the GGT-specific se...
probe. If the mRNA with the 22-base insertion is also present in the polysomal fraction, a second band should be detected. If the normal GGT mRNA is present in the polysomal fraction, we would expect only one band to be detected with a size corresponding to 81 bp when the oligo-control is used as a probe. As can be seen in Fig. 5A (upper panel, lane s) both bands are detected. Using the oligo-22 as a probe, we would expect no detectable band at 81 bp if only the normal GGT mRNA is present since it does not contain the complementary sequence to oligo-22. If the mRNA with the 22-base insertion is also present in the polysomal fraction, a band should be detected with a size corresponding to 103 bp. Such a band is present in Fig. 5A (lower panel, lane p). Contamination of the polysomal fraction by the supernatant is highly unlikely since (i) no bands were detected in the supernatant fraction (Fig. 5B, upper panel, lane s) and (ii) the measurement of lactate dehydrogenase in the supernatant amounted to 94% of the activity measured in the homogenized cells, whereas only 0.4% was found in the microsomes. Our results strongly support the idea that the 22-base insert-containing mRNA is translated in Hep G2 cells.

We have looked for both types of GGT mRNAs in a number of different human tissues using the same amplification procedures and probes. As evidenced by the presence of both the 81- and 103-bp band when oligo-control is used as a probe, and the 103-bp band when oligo-22 is used as a probe, both types of mRNAs are present in fetal liver, kidney, brain, intestine, stomach, placenta, mammary gland as well as in Hep G2 cells (Fig. 5B). The 103-bp band is also detected in adult liver following a longer exposure (data not shown).

**DISCUSSION**

We report here the cloning and characterization of two GGT-related cDNAs from human adult and fetal livers. These cDNAs exhibit some differences when compared with the other published cDNA sequences from human placenta (17), human fetal liver (18), or Hep G2 cells (19). The most striking difference is the presence of a 22-bp insertion in the GGT clones we have isolated. The insertion modifies the reading frame and alters the predicted translation product. Analysis of the sequence of the fetal liver cDNA reveals three large open reading frames starting with a methionine. Only two of these are surrounded by a consensus sequence usually observed for correct initiation of translation (31). We focused our attention on the first one since it corresponds to the ATG described for the heavy subunit of GGT. In this reading frame, the 22-bp insertion introduces a stop codon at position 1099. The putative truncated protein of 39,287 Da would consist mainly of the GGT heavy subunit differing only in the last 26 amino acids of the carboxyl-terminal portion. This protein would be devoid of any GGT activity since the catalytic activity is associated with the light subunit (32). The second open reading frame, out of phase with the first one, starts at position 1045 and would encode a protein of 24,108 Da (225 amino acids). This protein would encompass the complete sequence of the small GGT subunit since the NH$_2$-terminal part of the light chain of GGT (determined from human kidney (33)) corresponds to amino acid 37 on this protein (see Fig. 1). Nevertheless, although the initiator ATG is in a favorable context for translation (31) we have no evidence that this second open reading frame is utilized in vivo.

The translation of the first reading frame is highly likely due to the following lines of evidence. First, we demonstrate that this mRNA is found in microsomal polysomes. Second, a doublet has been already described for the heavy subunit of human kidney GGT following immunoprecipitation (34). These bands correspond to a glycosylated form of the protein with a $M_r$ of 53,000 and 50,000, respectively. The light species has been attributed to proteolytic degradation of the normal GGT heavy subunit (53,000). According to the present work, one can hypothesize that the core proteins are generated from the normal mRNA ($M_r$, 41,239) and from the insert containing mRNA ($M_r$, 39,287). Of particular relevance to our study is the fact that immunohistochemistry and histoenzymology of human GGT in liver (13) and in serum (12) do not exactly correlate. It has been proposed that either an inhibitor decreases the GGT activity (12) or that an altered form of GGT exists in human liver or in serum.

Altered proteins have already been observed in other sys-
tems such as in the case of human apolipoprotein B (35). A premature stop codon generates a protein of 350 kDa instead of the native form of 512 kDa. For GGT, a high molecular weight antigen with no activity has been observed in the rat (36). It has a molecular mass between 85 and 95 kDa and could not result from a truncated protein if one excludes an aggregation process. Such an aggregation has been observed for the purified small subunit of the rat kidney GGT (37).

We have no explanation for the fact that we have preferentially cloned cDNAs containing an extra 22 base pairs in the coding region. Although it has been shown in several cases that nonsense mutations correlate with a decrease in the weight antigen with no activity has been observed in the rat (36). It has a molecular mass between 85 and 95 kDa and could not result from a truncated protein if one excludes an aggregation process. Such an aggregation has been observed for the purified small subunit of the rat kidney GGT (37).

On the basis of sequencing results of a genomic clone, mRNAs containing the extra 22 bases could result from the use of an alternative 3′-acceptor site during splicing (Fig. 4) as already described for other systems (40, 41). In our case the on/off splicing regulation mechanism is not tissue-specific as demonstrated by polymerase chain reaction amplification. Both forms of mRNA are detected in the hepatoma cell line Hep G2, kidney, liver, brain, mammary gland, intestine, and stomach.

The 5′-noncoding region of our human fetal cDNA clone is unusually long (744 bp). In fact, most of the leader sequences on vertebrate mRNAs fall in the range of 20–100 nucleotides (31) if one excepts proto-oncogenes. Long leader sequences are not compatible with efficient translation, provided that any upstream open reading frame initiated on an ATG in a favorable context for initiation does not overlap with the main open reading frame. In the 5′-untranslated region of the fetal liver GGT mRNA, two ATG (~709, −31) are susceptible to open two short reading frames (18 and 16 amino acids) which terminate at positions −565 and −268, respectively, without any sparing effect on GGT mRNA translation.

The 5′-noncoding region characterized in the present study differs from those of the human placenta (17) and Hep G2 cells (19). In this region, homologous sequences are detected among the different cDNAs but at different positions with respect to the ATG. In humans we have characterized a multigene family for GGT (15), and it is possible that the different mRNAs are encoded by different genes. Nevertheless, such an organization in the 5′-noncoding region has already been observed in other systems where only one gene is active (42). Since it is not known whether these clones are full-length, there is insufficient information to conclude whether there might be a unique promoter or multiple promoters. A similar observation has been made for the unique rat GGT gene encoding GGT mRNAs varying in their 5′-untranslated region (43). Concerning the 3′-noncoding region, there are only differences in length between the polyadenylation signal AATAAA and the poly(A) tail. Such a microheterogeneity has been described for other mRNAs (44) and has not yet been linked to any regulatory processes.

Our results demonstrate a possible complex regulation of GGT genes in humans. Until now, only one modification in the processing of GGT has been described for Hep G2 cells (45) in which the precursor is not cleaved into two subunits. This is not due to an alteration in the primary sequence (19) but rather in a modification of the processing factors. We are now exploring the possibility that the human multigene family specific for GGT encodes altered primary polypeptide structures under different physiopathological conditions.

Acknowledgments—We thank Dr. R. Barouki for the synthesis of the different oligonucleotides and his advice. We thank Drs. Y. Laperche and J. Hanoune for their most helpful comments, K. Hehir for her help and guidance with some of the DNA sequencing, Dr. R. Wydro for some helpful suggestions, and L. Rosario and E. Aubenas for their skillful secretarial assistance.

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An alternatively processed mRNA specific for gamma-glutamyl transpeptidase in human tissues.
A Pawlak, E H Cohen, J N Octave, R Schweickhardt, S J Wu, F Bulle, N Chikhi, J H Baik, S Siegrist and G Guellaën

*J. Biol. Chem.* 1990, 265:3256-3262.

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