Cloning and Recombinant Expression of a Structurally Novel Human Secreted Phospholipase A2

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The nucleotide sequence reported in this paper has been submitted to the GenBank®/EBI Data Bank with accession number AF306567.

Abbreviations: Secreted phospholipase A2; sPLA2; POPC/G/S, 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-choline/glycerol/serine. A comprehensive abbreviation system for the various mammalian sPLA2s is used: Each sPLA2 is abbreviated with a lowercase letter indicating the sPLA2 species (m and h for mouse and human, respectively), followed by uppercase letters identifying the sPLA2 group (GIB, GIIA, GIIC, GIID, GIIE, GIIF, GIII, GV, GIX, GX, GXI, and GXII).
Mammals contain a diverse set of secreted phospholipases A₂ (sPLA₂s) which liberate arachidonic acid from phospholipids for the production of eicosanoids and exert a variety of physiological and pathological effects. We report the cloning, recombinant expression and kinetic properties of a novel human sPLA₂ which defines a new structural class of sPLA₂s called group XII. The human group XII (hGXII) cDNA contains a putative signal peptide of 22 residues followed by a mature protein of 167 amino acids that displays homology to all known sPLA₂s only over a short stretch of amino acids in the active site region. Northern blot and RT-PCR analyses show that the tissue distribution of hGXII is distinct from the other human sPLA₂s with strong expression in heart, skeletal muscle, kidney, and pancreas and weaker expression in brain, liver, small intestine, lung, placenta, ovaries, testis, and prostate. Catalytically active hGXII was produced in *E. coli* and shown to be Ca²⁺-dependent despite the fact that it is predicted to have an unusual Ca²⁺-binding loop. Like for the previously characterized mouse group IIE sPLA₂s, the specific activity of hGXII is low in comparison to those of other mammalian sPLA₂, suggesting that hGXII could have novel functions that are independent of its phospholipase A₂ activity.

Keywords: eicosanoid/signal transduction/ arachidonate release/ inflammation/ lipid mediator
Secreted phospholipases A\textsubscript{2} (sPLA\textsubscript{2}) are Ca\textsuperscript{2+}-dependent, disulfide-rich, 14-18 kDa enzymes that catalyze the hydrolysis of phospholipids at the \textit{sn} 2 position to release fatty acids and lysophospholipids (1-3). In mammalian cells stimulated with proinflammatory agonists, a subset of sPLA\textsubscript{2}s are involved in the release of arachidonic acid for eicosanoid production (4,5). The first mammalian sPLA\textsubscript{2} to be identified was the pancreatic sPLA\textsubscript{2}. This sPLA\textsubscript{2} is found at high levels in pancreatic juice, where it has a well-known function in the digestion of dietary phospholipids (6), but also at lower levels in lung, liver, spleen, kidney, and ovary where it has been proposed to play a role in cell proliferation, acute lung injury, cell migration, and endotoxic shock (7-9). The first non-pancreatic mammalian sPLA\textsubscript{2} to be identified was the group IIA enzyme which is expressed at high levels during inflammation (10), and is the principal bactericidal agent against Gram-positive bacteria in human tears (11).

In addition to the above evidence, it is becoming clear that sPLA\textsubscript{2}s are involved in a diverse set of physiological functions (7,12-14). In the last few years, 6 mouse and 5 human sPLA\textsubscript{2}s structurally related to GIB and GIIA sPLA\textsubscript{2}s (mGIIC, hGIID, mGIID, hGIIE, mGIIE, mGIIF, hGIIF, hGV, mGV, hGX, and mGX) have been identified (15-20) (Valentin et al., submitted for publication). All of these group I/II/V/X sPLA\textsubscript{2}s have similar primary structures, including identical catalytic site residues and partially overlapping sets of disulfides (21). However, they are not closely related isoforms since the level of amino acid identity is typically 20-50\% among these sPLA\textsubscript{2}s. More recently, a novel human group III sPLA\textsubscript{2} was identified (22), which is structurally distinct from the group I/II/V/X sPLA\textsubscript{2}s but related to the group III sPLA\textsubscript{2}s found in bee and lizard venoms. This diversity of sPLA\textsubscript{2} structures and the fact that the tissue distribution of the different sPLA\textsubscript{2}s are distinct argue for a diversity of physiological functions for these lipolytic enzymes.

It is also clear that mammals contain a collection of proteins that tightly bind...
sPLA2s. Two types of sPLA2 receptors (M- and N-type) and some other soluble sPLA2 binding proteins have been identified (7,13,21,23-25) and are likely to play a role in the physiological functions of mammalian sPLA2s and in the toxicity of a wide variety of myotoxic and neurotoxic sPLA2s found in reptile and invertebrate venoms. Very recently, the cell surface proteoglycan glypican was also identified as a sPLA2 binding protein able to facilitate arachidonic acid release by GIIA and GV sPLA2s in fibroblastic cells (26).

Because of the presence of a large collection of sPLA2s in both mammals and many reptile and invertebrate venoms, we have been searching nucleic acid databases for the presence of novel mammalian sPLA2s with homology to all known types of these enzymes including structurally distinct ones like the group IX sPLA2 (Conodipine-M) from the venom of the cone snail Conus magus (27). In this paper, we report the cloning, recombinant expression, tissue distribution, and enzymatic properties of a novel human sPLA2. Because this sPLA2 clearly belongs to a new structural class, we propose to name it human group XII sPLA2 (hGXII) to follow the recently identified group XI plant sPLA2s (21,28,29).
EXPERIMENTAL PROCEDURES

Molecular Cloning of hGXII sPLA2

Searching for mammalian and venom sPLA2 homologs in gene databases stored at the National Center for Biotechnology using the tBLASTn sequence alignment program (30) resulted in the identification of different human ESTs (Genbank BE271092, AW468813, AI189300) and a human genomic BAC clone (GenBank AC004067) that display low homology with various mammalian and venom sPLA2s (27). None of the ESTs were found to contain the full-length cDNA coding for the new sPLA2 candidate, but a putative complete open reading frame could be constructed from the alignment of the different ESTs and the appropriately spliced genomic sequence. A forward primer (5´-TTT-GCG-GCC-GCA-TAT-GGA-GCT-GGC-TGC-TGC-CAA-GT) and a reverse primer (5´-TTT-AAG-CTT-CTA-GAA-TCT-GTC-ACT-AGC-TGT-CGG-CAT-C) flanking the above open reading frame and containing appropriate restriction sites were used to amplify by RT-PCR the cDNA fragment coding for hGXII sPLA2. The expected 717 nucleotide hGXII cDNA fragment could be amplified from human fetal lung, pancreas and testis cDNAs (Clontech) using a Taq Pwo polymerase mixture (Hybaid, UK). The PCR fragments were digested with Not I and Xba I, ligated into the mammalian expression vector pRc/CMV neo (Invitrogen), and entirely sequenced. Several clones were found to be identical to the consensus sequence described above.

Recombinant Expression of hGXII sPLA2

The pRc/CMVneo-hGXII construct was used as template in a PCR reaction with a forward primer (5´-TTT-GGA-TCC-ATC-GAA-GGT-CGT-CAG-GAG-CAG-GCC-CAG-ACC-GAC), which contains a BamHI site and a factor Xa protease site (Ile-Glu-Gly-Arg) adjacent to the predicted N-terminal Gln residue of mature hGXII sPLA2 (Fig. 1) and the reverse primer given above. The purified PCR product was digested with BamHI and HindIII and subcloned in frame with the truncated glutathione
S transferase (~10 kDa) encoded by the modified pGEX-2T vector (pAB3), which has been previously used to express several sPLA2s in E. coli (17). Protein production in E. coli BL21, purification of inclusion bodies, and refolding and cleavage of the fusion protein with factor Xa were carried out as described (17). Cleaved hGXII was purified by high pressure liquid chromatography on a Spherogel TSK SP-5PW column (10 µm, 0.75 x 7.5 cm, Altex) using a gradient of 1% acetic acid to 1 M ammonium acetate over 50 min (elution at 28 min) and was further purified on a reverse phase column (Waters RP8 Symmetry Shield, 5 µm, 100 Å, 0.46 x 25 cm) using a gradient of 10-60% acetonitrile in water with 0.1% trifluoroacetic acid over 50 min (elution at 36 min). The hGXII preparation appeared 100% pure when analyzed by SDS-PAGE. MALDI-TOF (Applied Biosystems DE-Pro) was carried out in the linear mode using sinapinic acid.

Analysis of the Tissue Distribution of hGXII sPLA2. The presence of mRNA for hGXII sPLA2 in different human tissues was explored by northern blot and RT-PCR analyses. A human northern blot (Clontech catalog No. 7780-1) was probed as described previously (18) with a 32P-labeled riboprobe corresponding to the hGXII coding sequence. For RT-PCR, reactions were performed with an internal forward primer (5’-GCC TTT CCC ACG TTA TGG TT) and the reverse primer described above (200 ng each), Taq polymerase, and 1 µl of human cDNA as template (Human Multiple Tissue cDNA Panels I and II, Clontech cat. numbers K1420-1 and K1421-1). PCR was carried out at 94°C for 2 min followed by 45 cycles of 94°C/30 sec, 60°C/30 sec, 72°C/1 min, followed by 72°C for 5 min. PCR reactions were analyzed by Southern blotting using a [32P]-labeled hGXII oligonucleotide probe (5’-GGA TGT GGC TCT CCA CTG TT).

Kinetic Studies. Large unilamellar vesicles (0.1 µm) of POPC, POPG, and POPS (31) were used to measure the initial rates of hydrolysis by hGXII in Hank’s balanced salt solution with 1.2 mM CaCl2 and 0.9 mM MgCl2 using the fatty acid
binding protein assay (17). The pH-rate profile and Ca\textsuperscript{2+} dependency for the action of hGXII on POPG and POPC vesicles, respectively, were obtained as described (17).
RESULTS AND DISCUSSION

Molecular Cloning of a Structurally Novel Human sPLA2

Screening of nucleic acid databases with all known types of mammalian and venom sPLA2s (groups I, II, III, V, IX, and X) led us to identify various human ESTs and a large human BAC clone of 161,326 nucleotides coding for a putative novel sPLA2 (hGXII) that displays homology with other sPLA2s only in the active site region. A cDNA sequence containing a possible complete open reading frame was deduced from the alignment of the various ESTs and the genomic sequence and was then used to design primers for RT-PCR experiments with cDNA from various human tissues. The expected 717 nucleotide cDNA fragment containing an open reading frame of 567 nucleotides was amplified at a high level from human fetal lung cDNA and at lower levels from pancreas and testis cDNAs (not shown). The open reading frame was found to display some of the expected features for a sPLA2 (Fig. 1A). The initiator methionine is followed by a 22 amino acid sequence presenting the features of a signal peptide (32) and a mature protein sequence of 167 residues. The calculated molecular mass and pI values for the mature protein are 18,702.1 Da and 6.26, respectively, and no consensus site for N-glycosylation was found. Like several other sPLA2s, the mature hGXII sequence contains 14 cysteines and a central catalytic domain with a HD catalytic diad (Fig. 1B). Comparison of the 717 nucleotide cDNA sequence with the genomic sequence indicates that the hGXII sPLA2 gene is composed of at least 4 exons and 3 introns spanning about 15 kilobases in length. The human BAC clone containing the hGXII gene was also found to contain different Sequence Tagged Sites positioned at the 4q25 locus, thus assigning the hGXII gene to this location on chromosome 4. Further screening of the EST databases with the hGXII cDNA sequence led to the identification of several other ESTs partially coding for mouse (GenBank AA020156 and AA204520), rat (GenBank AW918074), and bovine (GenBank AW353546) GXII sPLA2s (Fig. 1A). A full-length
amino acid sequence coding for *Xenopus laevis* GXII sPLA₂ was deduced from the alignment of two ESTs (GenBank AW641606 and AW639634). Interestingly, the level of identity of this novel GXII sPLA₂ among species is very high (Fig. 1A) as compared to those of other sPLA₂s (18,21).

A blastp search with the amino acid sequence of hGXII sPLA₂ against the protein databases stored at the National Center for Biotechnology reveals matches to a variety of sPLA₂s from mammals, *C. elegans*, plants and animal venoms, suggesting that this protein belongs to the sPLA₂ family. The homology however appears to be weak (< 35% identity with blast scores lower than 35) and restricted to a short stretch of less than 60 amino acid residues containing the active site domain and the HD catalytic diad, indicating that the hGXII sPLA₂ is unique among all known sPLA₂s (Fig. 1B). The histidine of HD is thought to function as a general base to deprotonate a water molecule as it attacks the substrate ester carbonyl carbon, and the β-carboxyl group of the adjacent aspartate coordinates directly to the catalytic Ca²⁺ cofactor (6,33). Except for 3 cysteines in the active site consensus sequence CCXXHDXC which match those of other groups of sPLA₂s, the location of the other 11 cysteines residues in hGXII is distinct from that of other sPLA₂s (Fig. 1B). Since the structural arrangement of disulfides has been the main basis for designating the different sPLA₂ group numbers, the naming of the new sPLA₂ as hGXII seems appropriate.

The homology between hGXII and all known sPLA₂s is so low that it is difficult to find the Ca²⁺ binding loop, which is usually highly conserved and provides 3 of the 4 amino acid ligands for the catalytic Ca²⁺ (34). All mammalian group I, II, V, and X sPLA₂s contain 19 amino acid residues between the most N-terminal residue that serves as a ligand to the active site Ca²⁺ (i.e. His-27 of hGIIA) and the catalytic histidine (i.e. His-47 of hGIIA). In contrast, the corresponding distances for hGIII and plant GXI sPLA₂s are 25 and 23 residues, respectively. hGXII contains a
potential Ca\(^{2+}\) binding segment GCGSP with 23 residues between the N-terminal glycine and the putative catalytic histidine as shown in Fig. 1. This segment is perfectly conserved among all of the GXII proteins found in gene databases. The x-ray structures of groups I, II, and III sPLA\(_2\)s reveal that the Ca\(^{2+}\) loop contains the consensus segment X\(_1\)CG\(_1\)X\(_2\)G\(_2\). The backbone carbonyl oxygens of residues X\(_1\), G\(_1\), and G\(_2\) coordinate to Ca\(^{2+}\), and the backbone NH of G\(_1\) is proposed to donate a hydrogen bond to the carbonyl oxygen of the enzyme-susceptible substrate ester (33,35). The fact that this residue is glycine in catalytically active sPLA\(_2\)s and that mutating this residue to serine lowers catalytic activity by about 10- to 20-fold (35) argues that steric bulk is poorly tolerated at this position. The putative Ca\(^{2+}\)-coordinating segment of hGXII shown in Fig. 1B fits the consensus sequence of other sPLA\(_2\)s with the exception that G\(_2\) is a proline in hGXII. The prediction based on examination of the x-ray structures of sPLA\(_2\)s is that the hGXII Ca\(^{2+}\) binding segment should be functional. It contains G\(_1\), and the backbone carbonyl of the C-terminal proline can coordinate to Ca\(^{2+}\) since its three extra methylene, compared to glycine, are sterically allowed because of the location of this residue on the enzyme’s surface away from the substrate binding cavity. Interestingly, sPLA\(_2\) isozymes with relatively low sPLA\(_2\) activity from the venom of the banded krait also contain proline in place of G\(_2\) (36).

**Tissue Distribution of hGXII sPLA\(_2\)**

The tissue distribution of hGXII was first analyzed by hybridization at high stringency to a human northern blot (Fig. 2). hGXII is expressed as several transcripts including a major one of ~1.4 kilobase, which is abundant in heart, skeletal muscle and kidney. hGXII transcripts are also present at lower levels in brain, liver, small intestine, lung and placenta, and expressed poorly, if at all, in colon, thymus, spleen and peripheral blood leukocytes. Furthermore, analysis by RT-PCR with commercial human tissue cDNA panels indicates a pattern of hGXII expression that is consistent with the northern blot data.
and additionally shows that this sPLA$_2$ is strongly expressed in pancreas, and weakly in ovaries, testis, and prostate (not shown). The pattern of expression of hGXII thus appears distinct from that of other known human sPLA$_2$s (16,19,22) (Valentin et al., submitted for publication), suggesting specific function(s) for this novel sPLA$_2$.

**Recombinant Expression of hGXII and Enzymatic Properties**

A mammalian expression vector containing the full-length hGXII cDNA was first used to transiently transfected HEK293 cells. The amount of sPLA$_2$ activity (as measured with an assay using radiolabeled *E. coli* membranes (16)) secreted into the culture medium 1-5 days after transfection was barely above that measured in medium from cells transfected with vector lacking the hGXII insert, suggesting that hGXII may have a low specific activity. In order to further analyze if hGXII is a catalytically active sPLA$_2$, we expressed hGXII as a fusion protein in *E. coli*, and the inclusion body fraction was submitted to a refolding strategy previously used to produce catalytically active mGIID sPLA$_2$ (17). After digesting the fusion protein with factor Xa protease, hGXII was purified to homogeneity by HPLC and was found to migrate as a pure protein of about 18 kDa on a Laemmli SDS gel (not shown). Mass spectrometry analysis gave an experimental mass of 18,702.6 ± 0.5 Da, which agrees well with the mass of 18,702.1 Da calculated from the sequence of mature hGXII shown in Fig. 1A. This result indicates that all 14 cysteines are engaged in disulfide bonds, and thus it is assumed that recombinant hGXII is properly folded.

Recombinant hGXII was found to be a catalytically active sPLA$_2$ when assayed with the radiolabeled *E. coli* membrane assay (16) and with POPG, POPS, and POPC vesicles using the fatty acid binding protein assay (17). As shown in Fig. 3A, sPLA$_2$ activity toward POPC vesicles was strictly Ca$^{2+}$-dependent ($K_{Ca} = 30 ± 10$ µM). hGXII activity is maximal near pH 8.0 and decreases at higher and lower pHs (Fig. 3B). The decrease as the pH is lowered presumably reflects, in part, the...
protonation of the active site histidine. As for all mammalian sPLA2s examined so far, the enzymatic activity of hGXII on phosphatidylglycerol vesicles is highest (Fig. 3C), which probably reflects the tighter binding of hGXII to anionic vesicles (37). Although hGXII hydrolyzes POPC at only ~7% of the rate of POPG, this difference is small compared to the greater than 10^5-fold preference of hGIIA for POPG versus POPC (18). POPS is also a good substrate for hGXII (Fig. 3C).

Concluding Remarks

In summary, we cloned a novel catalytically active human sPLA2, called hGXII, that belongs to a new structural class, with homologs in other mammalian species and in *Xenopus laevis*. Since hGXII is expressed in a limited number of human tissues and has an expression pattern distinct from those of other human sPLA2s, it is not expected to carry out “housekeeping” functions in cells, but to have physiological function(s) distinct from those of other human sPLA2s. A sPLA2 gene cluster for the structurally similar hGIIA, hGIIC, hGIID, hGIIE, hGIIF, and hGV sPLA2s is present on human chromosome 1 (Valentin et al., submitted for publication), while structurally more distant hGIB, hGX, and hGIII sPLA2s lie on different chromosomes (chromosomes 12, 16 and 22, respectively), as also shown in this study for hGXII sPLA2 (chromosome 4). Recombinant expression of hGXII shows that it is a catalytically active, Ca^{2+}-dependent sPLA2. However, the specific enzymatic activity of hGXII appears very low compared to those of other mammalian sPLA2s (for example hGIB, hGIIA, hGV, hGX) and is comparable to the low specific activity reported for mGIIE sPLA2 (18). This may be the reason why hGXII sPLA2 was not detected in earlier biochemical studies, despite the fact that this protein may be expressed at significant levels, as the transcripts coding for this later are present in fairly high amounts in several human tissues (Fig. 2). It is also interesting to note that the putative GXII sPLA2 from zebrafish (*Danio rerio*) is represented in gene databases by several ESTs that all contain a leucine in place of histidine in the catalytic HD segment. This type of mutation suggests that the
zebrafish GXII sPLA₂ has very low or no catalytic activity, probably lower than that of hGXII sPLA₂. This in turn suggests that the catalytic activity of group XII sPLA₂s may not be critical for their physiological functions, and that they may act by serving as ligands for sPLA₂ binding proteins rather than by acting as lipolytic enzymes (13).

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REFERENCES

LEGEND TO FIGURES

FIG. 1. Alignment of the amino acid sequences of sPLA2s. Panel A, the full-length sequence of hGXII is aligned with the amino acid sequences of mouse, rat, bovine and Xenopus GXII sPLA2s (sequences were deduced from the alignment of different ESTs and from the BAC clone). For some sPLA2s, the XX residues indicate that the sequence is partial. Arrowhead indicates the predicted signal peptide cleavage site (32). The active site region containing catalytic site residues that are found in all sPLA2s, and the putative Ca²⁺ binding segment GCGSP are indicated. The level of identity between the mature protein sequence of hGXII and other GXII sPLA2s is shown. Panel B, alignment of the Ca²⁺-binding and active site regions of hGXII with a representative member of the four other structural classes of sPLA2s (hGIB for GI/II/V/X sPLA2s, hGIII for GIII sPLA2s, Conodipine-M for GIX sPLA2, and Rice II for GXI sPLA2s).

FIG. 2. Northern blot analysis of the tissue distribution of hGXII. A commercial northern blot containing 2 µg of poly (A)⁺ RNA from different human adult tissues was hybridized at high stringency with a ³²P-labeled hGXII RNA probe as described under “Experimental Procedures.” ske. muscle, skeletal muscle; small intest., small intestine; PBL, peripheral blood leukocytes; kb, kilobase.

FIG. 3. Enzymatic Properties of hGXII. Panel A, initial velocity for the hydrolysis of POPC vesicles containing a trace of 1-palmitoyl-2-[8,9-³H]palmitoyl-sn-glycero-3-phosphocholine (100,000 dpm of substrate per assay of 60 Ci/mmol labeled lipid) as a function of the Ca²⁺ concentration. Panel B, initial velocity for the hydrolysis of POPG vesicles containing a small amount of 1-palmitoyl-2-[8,9-³H]palmitoyl-sn-glycero-3-phosphoglycerol (100,000 dpm of substrate per assay of 60 Ci/mmol labeled lipid) as a function of pH. Panel C, initial velocity for the hydrolysis of large unilamellar vesicles (0.1 µm) of the indicated phospholipid. Additional assay details
have been reported elsewhere (17).
A

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