A New SUMO-1-specific Protease, SUSP1, That Is Highly Expressed in Reproductive Organs*

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A full-length cDNA encoding a SUMO-1-specific protease, named SUSP1, was identified and cloned for the first time from the human brain. Nucleotide sequence analysis of the cDNA containing an open reading frame of 3336 base pairs revealed that the protease consists of 1112 amino acids with a calculated molecular mass of 126,116 Da. Like yeast Ulp1, SUSP1 is a cysteine protease containing the well conserved His/Asp/Cys catalytic triad. SUSP1 expressed in Escherichia coli cells efficiently released SUMO-1 from SUMO-1-β-galactosidase fusion but not from other ubiquitin-like protein fusions, including Smt3-β-galactosidase, suggesting its role in the generation of matured SUMO-1 specifically from its precursors. Interestingly, reproductive organs, such as testis, ovary, and prostate, contained much higher amounts of SUSP1 mRNA than colon and peripheral blood leukocyte, whereas other tissues, such as heart and spleen, had little or none. In addition, confocal microscopy using green fluorescent protein:SUSP1 fusion showed that SUSP1 is exclusively localized to the cytoplasm of NIH3T3 and HeLa cells. These results suggest that SUSP1 may play a role in the regulation of SUMO-1-mediated cellular processes particularly related to reproduction.

Ubiquitin (Ub)\(^1\) is a highly conserved 76-amino acid polypeptide, which is involved in a variety of cellular processes, including regulation of intracellular protein breakdown, cell cycle regulation, signal transduction, transcription, and antigen presentation (1–3). This small protein is covalently ligated to a variety of target proteins through the action of a multi-enzyme system consisting of E1 (Ub-activating), E2 (Ub-conjugating), and E3 (Ub-ligating) enzymes (3–4). The proteins ligated to multiple units of Ub are then degraded by the 26 S proteasome (5). Recently, a number of other small molecules, so called Ub-like molecules (Ubls), have been identified (6, 7). These proteins are structurally related to Ub and can be ligated to target proteins in a similar manner with Ub (8). However, covalent attachment of Ubls does not result in degradation of the modified proteins (6–8). To date, several Ubls, such as SUMO-1/Smt3, NEDD8/Rub1, UCRP, and Fub, have been identified (6–8). Of these, the best characterized Ubl is the mammalian SUMO-1 (also called UBL1, sentrin, PIC1, GMP1, or SMT3c), which can be conjugated to a variety of cellular proteins, such as promyelocytic leukemia protein, Ran-GTPase-activating protein (RanGAP1), and inhibitor of nuclear factor-κB (IκBα) (9–11). SUMO-1 modification is implicated in the targeting of RanGAP1 to the nuclear pore complex (9, 10) as well as in stabilization of IκBα from degradation by the 26 S proteasome (11). Like Ub, all of the Ubls are synthesized as precursor proteins with one or more amino acids following the C-terminal Gly-Gly residues of the mature Ubl proteins (6, 7). Thus, the tail sequences of the Ubl precursors need to be removed by Ubl-specific proteases (Ulps) prior to their conjugation to target proteins. Li and Hochstrasser (12) have recently identified and cloned an Ubl-specific protease, called Ulp1 in yeast, which can generate the mature form of Smt3 and SUMO-1. Ulp1 shows no sequence similarity to any known deubiquitinating enzymes. Interestingly, this protease is required for G2/M phase progression of the cell cycle.

Recently, we have identified a new 30-kDa SUMO-1-hydrolase from extracts of bovine brain, which is different from the 72-kDa yeast Ulp1 (13). This enzyme can generate free SUMO-1 molecules not only from a SUMO-1-peptide fusion but also from RanGAP1-SUMO-1 conjugates, suggesting that the removal of SUMO-1 from its protein conjugates, like deubiquitination, may play an important role in regulation of SUMO-1-mediated cellular processes. In addition, a computer-assisted homology search in the cDNA data base reveals the existence of many different putative proteins having a conserved presumptive catalytic domain homologous to yeast Ulp1. Thus, it appears that a family of SUMO-1-specific proteases that are structurally related is universally distributed in a wide variety of eukaryotic cells. Here we report cloning and characterization of a new SUMO-1-specific protease, named as SUSP1, which is highly expressed in human reproductive organs.

EXPERIMENTAL PROCEDURES

DNA Manipulation—The KIAA0797 cDNA clone (GenBank\(^TM\) accession number AB018340), which contains a conserved putative catalytic domain homologous to yeast Ulp1 (12), was kindly provided by Dr. Takahiro Nagase (Kazusa DNA Research Institute, Japan). The 4128-bases in the complementary DNA of the KIAA0797 clone was subcloned into the pBluescript vector and inserted into the pET-11b expression vector. The recombinant plasmid was transformed into E. coli BL21 (DE3) (Novagen, Madison, WI), and the recombinant protein was expressed as a fusion with 6×His and cleaved with T7 protease (Amersham Pharmacia Biotech, Piscataway, NJ) when the expression level reached 10% of the total cellular protein.

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\(^{1}\) The abbreviations used are: Ub, ubiquitin; E1, ubiquitin-activating enzyme; E2, ubiquitin carrier protein; E3, ubiquitin-protein isopeptide ligase; Ubls, Ub-like molecules; RanGAP1, Ran-GTPase-activating protein; IκBα, inhibitor of nuclear factor-κB; Ulp, Ubl-specific protease; SUSP, SUMO-1-specific protease; PCR, polymerase chain reaction; PEST, MHSPPPEEPSEEEH; GST, glutathione S-transferase; GFP, green fluorescent protein.

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base pair SalI-NotI fragment of KIA0797 was cut off and ligated into the pBluescript II KS(1) vector. Because the clone lacks the 5'-sequence for the N-terminal 28 amino acids of SUSP1, the 5'-anchored PCR method using the 5'-RACE PCR kit (Life Technologies, Inc.) was employed to clone the ultimate 5'-end. The reactions were performed according to the manufacturer's instructions, and a 600-base pair product was obtained. The resulting plasmid containing the full-length cDNA was referred to as pBS/SUSP1. Several independent clones were sequenced on both DNA strands using an automated DNA sequencer to exclude any PCR error, and all restriction sites used for subcloning were verified as well.

To generate the plasmids expressing Ublz-galactosidase fusions, the SpeI restriction site was introduced immediately upstream of the ATG start codon for Ub in pACUbz-galactosidase (14) by PCR-based site-directed mutagenesis. The restriction sites for SpeI and BamHI were also introduced by PCR to the 5'- and 3'-regions of cDNAs for Ubls, respectively. The PCR products were cut out by SpeI and BamHI and ligated into pACUbz-galactosidase that had been treated with the same restriction enzymes. The plasmids expressing Fubz-galactosidase, Smt3z-galactosidase, and SUMO-1z-galactosidase were gifts from Drs. Rohan T. Baker (Australian National University), Erica S. Johnson (Rockefeller University), and Rohit Mahajan (Scripps Research Institute), respectively.

Preparation of Purified SUMO-1-PESTc and Smt3-PESTc—To obtain SUMO-1 and Smt3 having a C-terminal peptide extension of MHISPPEPESEEEEEHYC (referred to as PESTc) (17), the DNA fragments encoding SUMO-1zPESTc and Smt3zPESTc were synthesized using PCR and ligated into the expression vector pGEX-2T (Amersham Pharmacia Biotech). Extracts were prepared from Escherichia coli cells that had been transformed with the recombinant plasmids and loaded onto a glutathione-Sepharose 4B column equilibrated with phosphate-buffered saline. After washing with the same buffer, the column was treated with thrombin to cleave off glutathione-S-transferase (GST) that is fused to the N termini of SUMO-1zPESTc and Smt3zPESTc. The proteins were then eluted with the same buffer and subjected to gel filtration on a Sephadex G-75 column to remove thrombin.

Expression of SUSP1 in E. coli—The E. coli JM109 cells were transformed with pBS/SUSP1 and grown to a late exponential phase at 37 °C.

Fig. 1. Nucleotide sequence of the cDNA for SUSP1 and deduced amino acid sequence of the SUSP1 protein. The nucleotides are numbered on the right, beginning at the A of the presumed start codon. The amino acid residues are also numbered on the right. The asterisk indicates the TGA stop codon. (GenBank™ accession number AF196304).
in Luria broth containing ampicillin. The cultures were then treated with isopropyl-thio-β-D-galactoside to 2 mM and further incubated for the next 3 h. After incubation, the cells were collected and resuspended in 25 mM Tris-HCl buffer (pH 7.8) containing 5 mM 2-mercaptoethanol, 1 mM EDTA, and 10% (v/v) glycerol. They were then disrupted by the French press at 14,000 p.s.i. and centrifuged at 100,000 × g for 2 h. The resulting supernatants were chromatographed on a DEAE-Sepharose column equilibrated with the same buffer. After washing the column, the bound proteins were eluted with a linear gradient of 0–0.3 M NaCl. Aliquots of the fractions were assayed for the SUSP1 activity on SUMO-1-β-galactosidase fusion (see below), and the fractions with high activity, which eluted at about 0.2 M NaCl, were pooled and used for further studies.

*In Vitro Assay for SUSP1 Activity*—To assay the activity of SUSP1 in *vitro*, extracts were prepared as described above from the *E. coli* MC1000 cells transformed with the plasmids expressing Ubβ-galactosidase fusions. The partially purified SUSP1 (20 μg) from the DEAE-Sepharose chromatography was then incubated for 2 h at 37 °C in the absence and presence of the extracts containing Ubβ-galactosidase fusions (50 μg), purified SUMO-1-PESTc (5 μg), or Smt3-PESTc (5 μg). Reaction mixtures in total volumes of 50 μl also contained 100 mM Tris-HCl, (pH 7.8), 1 mM dithiothreitol, 1 mM EDTA, and 5% glycerol. After incubation, the reaction was terminated by adding 20 μl of 10% (v/v) SDS and subjected to polyacrylamide gel electrophoresis under denaturing conditions (15). To determine the cleavage of Ubβ-galactosidase, immunoblot analysis was performed using an anti-β-galactosidase antibody. For assaying the cleavage of SUMO-1-PESTc and Smt3-PESTc, the gels were directly stained with Coomassie Brilliant Blue R-250.

To assay the activity of SUSP1 on RanGAP1-SUMO-1 conjugates, GST-SUMO-1-modified 35S-RanGAP1 and 35S-RanGAP1, respectively. D, effects of various protease inhibitors on the hydrolysis of SUMO-1-β-galactosidase. The SUSP1 enzyme preparation (20 μg) was incubated with the extracts containing SUMO-1-β-galactosidase (50 μg), purified SUMO-1-PESTc (5 μg), or Smt3-PESTc (5 μg) for various periods. The cleavage of SUMO-1-β-galactosidase was assayed as above, and that of SUMO-PESTc and Smt3-PESTc was assayed by staining the gels with Coomassie Brilliant Blue R-250. The numbers on top of each gel indicate the incubation period. C, hydrolysis of RanGAP1-SUMO-1 conjugates. The extracts containing SUSP1 and Ulpl and GST-SUMO-1-modified 35S-RanGAP1 were prepared as described under “Experimental Procedures.” Reaction mixtures (total 36 μl) containing 15 μl of the enzyme preparations and 4 μl of the labeled substrate were incubated for 3 h at 37 °C. The substrate alone was also incubated as a control (− lane). The samples were then subjected to SDS-polyacrylamide gel electrophoresis followed by autoradiography. RanGAP1–SUMO-1 and RanGAP1 indicate GST-SUMO-1-modified 35S-RanGAP1 and 35S-RanGAP1, respectively.

RESULTS AND DISCUSSION

**Cloning of a cDNA Encoding SUSP1**—The open reading frame specifying a human SUMO-1-specific protease was identified and designated as SUSP1. Baker et al. (16) have recently suggested the nomenclature for human Ub-specific protease as USP. By adopting the nomenclature system, we named this putative SUMO-1-specific protease as SUSP1. The 5’-end of the cDNA for SUSP1 was obtained through the 5’-anchored PCR technique using the KIAA0797 cDNA clone, which lacks the 5’-sequence for the N-terminal 28 amino acids of SUSP1. The

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position of the ATG start codon was inferred to yield the 3336-base pair open reading frame, which suggest that the full-length cDNA clone encodes a protein of 1112 amino acids with a calculated molecular mass of 126,116 Da and an isoelectric point (pI) of 6.30 (Fig. 1). Like yeast Ulp1 and the related putative enzyme Ulp2 (equivalent to Smt4) (12), SUSP1 as well as the other putative human SUSPs, SUSP2 and SUSP3 (GenBank accession numbers AF199458 and AF199459, respectively), have well conserved residues of the catalytic triad (His, Asp, and Cys) and an invariant Gln residue predicted to help to form the oxyanion hole in the active site (Fig. 2). However, the sequence similarity was largely restricted to the conserved active site domains. In addition, SUSP1 showed no evident amino acid sequence similarity to any known deubiquitinating enzymes. On the other hand, it has recently been reported that the partial peptide sequence of an enzyme processing UCRP, a member of Ulpfs, from human lung carcinoma cells shows a significant similarity to yeast Ub-specific protease, Ubp1 (18). Thus, it is likely that SUSPs described in the present study form a novel family distinct from USPs and UCRP-processing enzymes.

Substrate Specificity of SUSP1—To determine whether SUSP1 is capable of cleaving the carboxyl side of the C-terminal Gly-Gly residues of SUMO-1, the partially purified enzyme was incubated with SUMO-1-\beta-galactosidase fusion as a model substrate. We also examined whether the enzyme preparation could cleave other Ub-\beta-galactosidase fusions. As shown in Fig. 3A, SUSP1 efficiently released SUMO-1 from SUMO-1-\beta-galactosidase. However, it showed little or no activity on any other Ub-\beta-galactosidase fusions, including Smt3-\beta-galactosidase. It also could not release free Ub from Ub-\beta-galactosidase. To confirm the ability of SUSP1 in cleaving SUMO-1-\beta-galactosidase, the enzyme was incubated with the substrate as above but for varying periods. As shown in Fig. 3B (top panel), SUSP1 cleaved SUMO-1-\beta-galactosidase in a time-dependent fashion.

Smt3 is a yeast homolog of mammalian SUMO-1 (6, 7). In addition, it has been demonstrated that yeast Ulp1 is capable of cleaving Smt3-hemagglutinin fusion as well as SUMO-1-hemagglutinin (12). Because the Smt3 precursor has a much smaller C-terminal extension than Smt3-\beta-galactosidase, we examined whether SUSP1 might be able to release Smt3 from its fusion with a small peptide, such as Smt3-PESTc. As a control, we also used SUMO-1-PESTc as a substrate. Fig. 3B shows that SUSP1 cleaves SUMO-1-PESTc in a time-dependent fashion (middle panel) but not Smt3-PESTc at all (bottom panel). These results suggest that SUSP1 shows a tight substrate specificity for interaction only with SUMO-1.

We then examined whether SUSP1 might be capable of releasing SUMO-1 from RanGAP1-SUMO-1, using GST-SUMO-1-modified 35S-RanGAP1 as a substrate, in which GST-SUMO-1 is conjugated to RanGAP1 through an isopeptide linkage. Whereas yeast Ulp1 efficiently cleaved GST-SUMO-1-modified RanGAP1 in accord with the earlier report (12), little or no hydrolysis of the substrate was observed with SUSP1 (Fig. 3C). Thus, SUSP1 appeared unlikely to process RanGAP1-SUMO-1. However, the lack of the isopeptidase activity of SUSP1 could not be rigorously concluded from the negative in vitro result. The enzyme might not be properly folded under the conditions it was expressed or may require modification or interaction with other factors in human cells to act on the RanGAP1p-SUMO-1 conjugate.

Like Ulp1 and Ulp2 in yeast (12), SUSP1 contains one conserved cysteine residue in the putative active site domain (see Fig. 2). Therefore, we examined whether sulphydryl-blocking reagents could prevent the enzyme activity. Cleavage of SUMO-1-\beta-galactosidase was completely blocked by incubation of the partially purified SUSP1 with 5 mM N-ethylmaleimide or iodoacetamide (Fig. 3D). On the other hand, little or no inhibition was observed upon treatment with 5 mM phenylmethylsulfonyl fluoride, an inhibitor of serine proteases, or o-phenanthroline, a metal chelating reagent. Ub-aldehyde, a specific inhibitor of deubiquitinating enzymes, could not inhibit the SUSP1 activity on SUMO-1-\beta-galactosidase (data not shown). These results are consistent with SUSP1 being a cysteine protease. This conclusion is supported by the earlier report on yeast Ulp1 (12), which showed by mutagenesis that the suspected Cys residue is crucial and that the enzyme bears significant sequence homology to the adenovirus cysteine protease.

Expression of SUSP1 mRNA in Human Tissues—Northern blot analysis using a human SUSP1 cDNA as a probe detected a single transcript of about 4.4 kilobases in various human tissues. The size of the human SUSP1 cDNA, consisting of 3336 base pairs and a poly(A) tail, corresponded well with the estimated size of the transcript (Fig. 4). Interestingly, expression of the SUSP1 mRNA was the highest in reproductive organs with the order of testis, ovary, and prostate. Peripheral blood leukocyte and colon also expressed SUSP1 mRNA but to relatively less extents. On the other hand, little or no signals were detected from other human tissues, including brain, liver, lung, kidney, pancreas, spleen, thymus, heart, and skeletal muscle under the same experimental conditions (data not shown), despite the fact that the original cDNA clone for SUSP1 was obtained from human brain. However, we could detect faint signals in brain and small intestine but not in others upon prolonged exposure of the same mRNA blots. Thus, it appears that expression of the SUSP1 mRNA is tissue-specific, partic-
ularly in reproductive organs. These results suggest that SUSP1 may play an important role in reproductive processes.

Subcellular Localization of SUSP1—To explore the distribution of SUSP1 in cells, the plasmids expressing GFP alone or GFP-SUSP1 fusion were transfected to NIH3T3 and HeLa cells. Upon observation of the cells under a confocal microscope, control GFP was found in both the nucleus and the cytoplasm of NIH3T3 cells, as typical small proteins, like GFP, diffuse into nearly all of subcellular organelles (Fig. 5A). On the other hand, the GFP-SUSP1 fusion protein was almost exclusively found in the cytoplasm (Fig. 5B). Similar data were obtained with HeLa cells (data not shown). Thus, it appears likely that SUSP1 functions primarily in the cytoplasm.

RanGAP1 is targeted from the cytoplasm to the nuclear membrane upon modification by SUMO-1, thus playing an essential role in nuclear transport of proteins (10). SUMO-1 is also involved in negative regulation of the nuclear factor-κB pathway by being conjugated to IκBα, thus preventing ubiquitination of IκBα and nuclear translocation of nuclear factor-κB from the cytoplasm (11). In addition, it has recently been demonstrated that SUMO-1 modification is involved in a variety of other cellular processes, including activation of the transcriptional response of p53 tumor suppressor (19, 20), targeting of the homeodomain-interacting protein kinase 2 to nuclear dots (21), and regulation of septin ring dynamics during cell cycle (22, 23).

The 30-kDa SUMO-1 hydrolase from bovine brain (13) as well as yeast Ulp1 (12) have been shown to release SUMO-1 from RanGAP1-SUMO-1 conjugates. Although in the present study we could not demonstrate the isopeptidase activity of SUSP1 on RanGAP1-SUMO-1, it is possible that SUSP1, located almost exclusively in the cytoplasm, may act on SUMO-1-modified IκBα as well as on other SUMO-1-modified proteins that have not yet been identified.

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