Peptide Sequence Analysis and Molecular Cloning Reveal Two Calcium Pump Isoforms in the Human Erythrocyte Membrane*

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The sequence of more than 1,000 amino acid residues, derived from two different isoforms, has been determined from peptides generated from purified human erythrocyte membrane Ca**+ATPase (hPMCA). Several of these peptide sequences correspond to the previously reported, cDNA deduced sequence of the "teratoma" Ca**+ pump isoform hPMCA1 (Verma, A. K., Filoteo, A. G., Stanford, D. R., Wieben, E. D., Penniston, J. T., Streher, E. E., Fischer, R., Heim, R., Vogel, G., Matthews, S., Streher-Page, M.-A., James, P., Vorherr, T., Krebs, J., and Carafoli, E. (1988) J. Biol. Chem. 263, 14152-14159). The complete primary structure of a novel isoform (hPMCA3) has been determined by molecular cloning and nucleotide sequencing of its corresponding cDNA. This new member of the plasma membrane Ca**+ pump family consists of 1,205 amino acid residues with a calculated M, of 133,930, and it shows 88% similarity (75% identity) with the previously sequenced pump isoform. Specific probes detect major mRNA species of 5.6 kilobases for hPMCA1, and of 7.5 kilobases for hPMCA3, on Northern blots of human K562 erythroleukemic cell RNA. A large number of peptide sequences match perfectly with only one or the other of these isoforms and all peptides (with 6 exceptions corresponding to a contaminant protein or to a third minor Ca**+ pump isoform) are found in either only one or in both of the isoforms. The two erythrocyte Ca**+ pumps display high sequence divergence in a few localized regions that may determine isoform-specific functional specializations; for example, the putative extracellular loop separating transmembrane domains 1 and 2, the highly negatively charged region previously suggested to be involved in Ca**+ binding, and the site of cAMP-dependent protein kinase phosphorylation.

The precise control of the intracellular free Ca**+ concentration is a prerequisite for the signalling function of Ca**+ in eukaryotic cells. Ca**+ pumps of the cell plasma membrane are a key role in this process by being capable of removing Ca**+ from the cells against very large concentration gradients (for reviews, see Schatzmann 1982; Carafoli, 1987). Recent studies involving molecular cloning methods have led to the determination of complete primary amino acid sequences for plasma membrane Ca**+ pumps from rats (Shull and Greerb, 1988) and humans (Verma et al., 1988). It has become clear from these studies that various isoforms exist for this protein which, at least in mammals, are encoded by a multigene family. Ca**+ pump isoform diversity appears to be further increased by alternative RNA splicing of single-gene transcripts (Strehler et al., 1989). Nothing is known, however, about the functional significance and the possible tissue-specificity of these Ca**+ pump isoforms. Furthermore, it is not yet clear whether a given cell type can express more than one specific pump isoform, either sequentially or concomitantly.

Here we present evidence for the existence of two different Ca**+ pump isoforms in human erythrocytes. The conclusion is based on extensive sequence analysis of peptides of the purified human erythrocyte Ca**+ pump, and on molecular cloning and cDNA sequencing studies that have resulted in the identification and complete sequence determination of a novel human plasma membrane Ca**+ pump isoform.

MATERIALS AND METHODS

Enzymatic and Chemical Cleavage of Calcium Pump Protein and Peptide Purification and Sequencing—The enzyme was purified from erythrocyte ghosts as previously described (Niggl et al., 1979). ATPase modification and separation of peptides from tryptic, CNBr, and Staphylococcus aureus V8 digests were carried out as described before (Filoteo et al., 1987; James et al., 1988, 1989). Cleavage at tryptophan residues was performed according to Huang et al. (1983). Peptides were isolated by SDS-polyacrylamide gel electrophoresis and electrophoretic and cloning methods have led to the identification and complete sequence determination of a novel human plasma membrane Ca**+ pump isoform.

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Isolation and Sequence Analysis of Human Erythrocyte Calcium Pump Isoforms—To obtain as much primary amino acid sequence data as possible for the human red cell membrane Ca\(^{2+}\)-ATPase(s), large quantities of this protein (30 mg or more) were prepared (Niggli et al., 1979). The duration of the Ca\(^{2+}\) washout of the calmodulin column was extended to 18–24 h to ensure that the isolated pump was in a highly purified state. The protein was then subjected to various further chain modification, and cleavage conditions (see “Materials and Methods”) to obtain shorter peptides suitable for direct sequence determination. From the course of the peptide work it became clear that the human erythrocyte Ca\(^{2+}\) pump protein consists of a mixture of several (at least two) different isoforms. While many peptide sequences generated from the erythrocyte protein show identity to corresponding regions of the previously reported Ca\(^{2+}\) pump isoform (Fig. 1; Verma et al., 1988) an equal proportion clearly differ at several positions from those present in the cloned pump (see below).

Isolation and Sequence Analysis of cDNAs Corresponding to a Novel Human Plasma Membrane Calcium Pump Isoform—Although sequences of different isoforms have been deduced for the rat plasma membrane Ca\(^{2+}\) pump (Shull and Groth, 1988), the complete amino acid sequence of only a single isoform for the human enzyme has been reported so far (Verma et al., 1988). Since peptide work on the erythrocyte protein had indicated the existence of at least two isoforms (see above), various human cDNA libraries were screened under moderate stringency conditions with probes from the previously reported Ca\(^{2+}\)-ATPase cDNA. A 2.2 kb EcoRI probe covering amino acid codons 466–1193 (nucleotide positions 1395–3578 in Verma et al. (1988)) was first used to isolate a weakly cross-hybridizing cDNA (clone λH141.1) from a human small intestinal mucosa λZap cDNA library. An overlapping clone (λA3.1) containing identical nucleotide sequences but with an extension of about 0.7 kb towards the 5' end (and 71 bp shorter at the 3' end) was then also isolated from the human teratoma cell λgt10 cDNA library (Fig. 2A).

The nucleotide and deduced amino acid sequence of these cDNAs suggested that they correspond to a part of a novel isoform of the human plasma membrane Ca\(^{2+}\)-ATPase, showing a high degree of similarity (88% using the “Bestfit” version of the University of Wisconsin Genetics Computer Group software) to the amino acid sequence of the previously reported “teratoma” enzyme (Verma et al., 1988). This latter pump sequence corresponds to the rat isoform PMCA1 (Shull and Groth, 1988), albeit to a variant generated from an alternatively spliced transcript (Strehler et al., 1989). The human teratoma pump isoform will therefore from now on be called hPMCAl1 (the previously reported rat protein should then be called rPMCAla to indicate its generation from an alternatively spliced transcript of the corresponding rat gene).

The amino acid sequence encoded by the new human cDNA clones shows 86% similarity to the rat PMCA2 (rPMCA2), suggesting that these clones encode a third, as yet unidentified member of the plasma membrane Ca\(^{2+}\) pump family (hPMCA3). These clones encode the (COOH-terminal) portion of the molecule that has previously been identified as the “regulatory” region containing the calmodulin-binding domain typical of this type of ATPase (James et al., 1988; Verma et al., 1988). Overlapping cDNA clones covering the entire protein coding region of the corresponding mRNA were then isolated by further screenings of the human teratoma cDNA library with the 140-bp EcoRI-PstI 5' end subfragment of clone λA3.1. Of the several cDNA clones isolated (Fig. 2A), clones λA3.1 and λA3.4c together cover the entire protein coding sequence as displayed in Fig. 2B. The long open reading frame encoding the molecule is preceded by 397 nucleotides of 5' untranslated sequence and followed by 467 nucleotides of the 3' untranslated sequence (not counting 398 nt 5' untranslated sequence and 46 nt 3' untranslated sequence). This is also suggested by the size of the Ca\(^{2+}\) pump mRNA as detected on Northern blots made with RNA isolated from human K562 erythroleukemia cells (Fig. 3). While a hPMCA1-specific cRNA probe covering nucleotides 3195–3853 of the published sequence (Verma et al., 1988) detected a major band of about 5.6 kb (Fig. 3A), a probe specific for the novel isoform hPMCA3 (covering nucleotide positions 3064–3859 in Fig. 2) hybridized to a major mRNA species of about 7.5 kb (Fig. 3B). The mRNA for the hPMCA3 isoform is considerably longer than the cDNA sequence reported in Fig. 2B, indicating the presence of extended untranslated sequences in this molecule.

DNA Subcloning and Nucleotide Sequencing—cDNA fragments were subcloned into pUC18 and M13mp18/19 vectors (Pharmacia LKB Biotechnology Inc.) according to standard methods (Maniatis et al., 1982). The dinucleonucleotide chain termination method (Saengger et al., 1977) was applied to either single-strand M13 template DNA (Messing, 1983) or to denatured pUC plasmids (Zhang et al., 1986; Kraft et al., 1986), using the sequencing kit and “Sequenase” version 2.0 enzyme from United States Biochemical Co. (Cleveland, OH) according to the manufacturer's recommendations. About 75% of the sequence was obtained from both strands, and about 50% of the templates were sequenced more than once, using both dGTP and dITP reaction mixtures. Sequences were analyzed with the University of Wisconsin Genetics Computer Group sequence analysis software (Devereux et al., 1984) (Version 6, April 1989).
FIG. 1. Alignment of human erythrocyte membrane calcium pump peptides with the cDNA-de
duced hPmCA1b amino acid sequence (Verma et al., 1988). The top line shows the complete Ca" pump se-
quence in one letter code. Asterisks denote residues that differ in the novel erythrocyte Ca'+ pump isoform. The
method of peptide generation is indicated: c, CNBr cleavage; t, trypsin cleavage; u, V8 protease cleavage; w, trypto-
phan-specific cleavage. x denotes unidentified or missing cycles, and an arrow at the end of a sequence indicates that
the peptide was longer but further resi-
du were difficult to identify. Inferred
methionine residues of CNBr peptides
are displayed in lower case.

The Novel Sequence Represents One of the (Two) Major
Calcium Pump Isoforms of Human Erythrocyte Membranes—
A comparison of the novel primary structure described above
with the peptide sequences obtained from direct sequencing
of the erythrocyte protein showed that almost all the peptides
that failed to match perfectly to the sequence of the first
human pump isoform described (Verma et al., 1988) could
now be identified in the isoform described here (Fig. 4). The
fact that about 50% of all peptides match perfectly only with
the novel sequence, whereas about 30% are specific for the
first (hPmCA1b) isoform and about 20% are found in both
sequences, clearly indicates that the newly described protein
is a major Ca"+ pump isoform of human erythrocytes. In Figs.
1 and 4 an asterisk beneath an amino acid residue indicates
sequence divergence between the two isoforms at that posi-
tion: judging from the Figures, particularly clear isoform-
specific peptides are, e.g. V8 505-515, CNBr 586-594, V8 786-
792, CNBr 1146-1180, and CNBr 1200-1208 for the previ-
ously sequenced isoform (Verma et al., 1988, Fig. 1), and
CNBr 7-13, CNBr 15-26, CNBr 27-30, CNBr 477-506,
CNBr 589-612, W 1043-1076, CNBr 1132-1153, and V8 1162-
1177 for the isoform described here (Fig. 4).

A combined total of more than 1000 amino acid residues
has been determined by direct peptide sequencing for the
erythrocyte Ca"* pump isoforms (not counting overlapping
residues). Of the >70 individual peptide sequences only 6
could not be matched to either of the two cDNA deduced
sequences. These peptides could either stem from contami-
nating protein(s) in the erythrocyte Ca"*-ATPase preparation
or they might correspond to yet another Ca"* pump isoform
in these preparations.

Structural Features of the Novel Isoform—The two human
Ca"* pump isoforms display 75% sequence identity and 88%
amino acid sequence similarity (using the Bestfit program of
Fig. 2. Structure, nucleotide sequence and encoded amino acid sequence of cDNA clones specifying a novel plasma membrane calcium pump hPMCA3. A, top: schematic representation of overlapping cDNA clones isolated from a human intestinal mucosa (λint5.1) and a human teratoma cDNA library (λ3.1, λ3.5c, λ3.5c0). Restriction enzyme cutting sites are indicated. B, EcoRI; H, HindIII; F, PstI; S, SacI. EcoRI sites artificially created by linker addition are indicated by a broken line. Bottom: scheme of the combined cDNA showing the regions corresponding to 5' and 3' untranslated sequences as open boxes and the protein-coding part as filled box. ATG and TGA, position of translational initiation and stop codon, respectively. B, combined nucleotide and encoded amino acid sequence of cDNA clones λ3.5c and λ3.1. The first nucleotide of the ATG initiation codon is at position +1, 5' untranslated sequences are negatively numbered. The EcoRI linker sequences present at either end are shown in italics. The 10 hydrophobic domains possibly spanning the membrane are underlined. The residue D 185 and K 291 corresponding to the site of phosphorylated intermediate formation and flavoseerin isothiocyanate-(ATP-) binding, respectively, are shown in bold face and are underlined. The cryptic polyadenylation signal TATAAA is also underlined.
Erythrocyte Membrane Calcium Pump Isoforms

Fin. Z-continued

Fig. 3. Northern blot analysis of human erythrocyte calcium pump mRNAs. A, 5 μg of poly(A)+ RNA from human erythrocytic leukemia K562 cells was probed with an antisense cRNA specific for the published (Verma et al., 1988) Ca2+ pump isoform hPMCAlb. B, 20 pg of total RNA from human erythroleukemic K562 cells were probed with a cDNA fragment specific for the novel Ca2+ pump isoform hPMCA3. The position of RNA size markers and of 28 S RNA is indicated at the left. Heavy arrows indicate the position of major mRNA species at 5.6 kb in A and at 7.5 kb in B.

the University of Wisconsin Genetics Computer Group software), thus conforming to the values observed for the isoform variability among other ion-transporting ATPases (Brandl et al., 1986; Shull et al., 1986; Shull and Greeb, 1988; Lytton and MacLennan, 1988; Gunteski-Hamblin et al., 1988). Closer inspection of the two sequences shows that divergences are not equally distributed along the entire length of the proteins. Instead, regions of high sequence divergence coexist with others of almost total sequence conservation (see Figs. 1 and 4).

As would be expected, the domains of known functional importance are highly conserved. This applies not only to the region encompassing the site of acylphosphate formation (Asp105 in the novel isoform) and to the fluorescein isothiocyanate (ATP-) binding site (Lys120), but also to sequences previously shown to be highly conserved among ion-transporting ATPases (Verma et al., 1988; Serrano, 1988). In addition, a surprisingly high degree of sequence conservation is apparent in the 10 hydrophobic regions that may correspond to the membrane-spanning domains of the plasma membrane Ca2+-ATPase (indicated in Fig. 2B for the novel isoform).

The sequence divergence is especially high in the NH2-terminal (residues 1–60) and the COOH-terminal regions (residues 1130–1210 and 1115–1193, respectively, for the two isoforms). While no particular function has as yet been attributed to the NH2-terminal portion, the COOH-terminal region has been shown to contain regulatory domains crucially involved in the function of the ATPase (Pedersen and Carafoli, 1987; James et al., 1988, 1989; Verma et al., 1988; Shull and Greeb, 1988; Vorherr et al., 1989). Although the primary sequence of the calmodulin-binding domain proper is highly conserved in the two isoforms (residues 1100–1127 in hPMCAlb [James et al., 1988; Verma et al., 1988] and residues 1087–1113 in the hPMCA3 isoform described here), the regions immediately COOH-terminal to the domain are highly divergent. In hPMCAlb the site of phosphorylation by the CAMP-dependent protein kinase has been identified within this COOH terminal region (Ser110 in the consensus-type sequence R110KRNSSS112) (James et al., 1989); however, no corresponding sequence is present in the COOH-terminal region of the new isoform. Although a plausible target site for the CAMP-dependent kinase (110DKAS112) is present elsewhere in the COOH-terminal region of the novel isoform, it is well possible that the second isoform cannot be phosphorylated by this enzyme (see “Discussion”). Thus, while both isoforms clearly represent Ca2+ pumps of the plasma membrane, they differ sufficiently from each other in some regions to suggest differences in their functional and regulatory properties.

DISCUSSION

Characterization of a Novel Member of the Plasma Membrane Calcium Pump Family—The CDNA deduced amino acid sequence reported in this paper provides the second complete
primary structure for a human plasma membrane Ca\textsuperscript{2+}-ATPase. Two complete sequences are also known for the rat enzyme (Shull and Greeb, 1988), as well as a partial (COOH-terminal) sequence for a bovine calcium pump (Brandt et al., 1988). Sequence comparisons indicate the existence in mammals of at least three to four different plasma membrane Ca\textsuperscript{2+}-ATPase isoforms which are the products of separate genes. The previously reported human sequence (Verma et al., 1988) corresponds to the rat isoform rPMCA1 (Shull and Greeb, 1988) and will therefore now be termed hPMCA1. These two proteins are >99% identical in their first 1117 amino acids and only differ in their COOH termini. This difference, however, is due to differential RNA splicing involving a single exon towards the COOH-terminal end of the corresponding gene (Strehler et al., 1989). To differentiate between these closely related variants we suggest that the rat isoform be called rPMCAla and the human protein hPMCAlb. On the other hand, the novel human isoform reported here does not correspond to the second rat isoform rPMCA2 (Shull and Greeb, 1988) since the degree of similarity between these two proteins (86%) is comparable to that obtained from a comparison of the two human isoforms. Moreover, a human cDNA clone encoding a Ca\textsuperscript{2+} pump isoform (hPMCA2) corresponding to the rat rPMCA2 protein has recently also been isolated in our laboratory.\textsuperscript{2} Considering the very high degree of sequence divergence among different Ca\textsuperscript{2+} pump isoforms in their COOH-terminal regions (see "Results"), the 65% identity found between the last 71 residues of the hPMCA3 isoform and the available portion of the bovine pump isoform (Brandt et al., 1988) might indicate that these two isoforms correspond to each other. However, a value of 65% identity is still considerably lower than that for the average identity between the two "bona fide" human pump isoforms (75%),

\textsuperscript{2} R. Heim, R. Fischer, and E. E. Strehler, unpublished results.
implying that the bovine Ca\(^{2+}\) pump may correspond to a fourth mammalian isoform.

**Two Isoforms of the Plasma Membrane Calcium Pump in Human Erythrocytes**—Peptide sequences have been obtained from purified human erythrocyte Ca\(^{2+}\)-ATPase protein(s) that specifically match either one or both of the human cDNA deduced pump sequences. As mentioned, the 8 peptides, out of a total of more than 70, that could not be matched to one (or both) of the two human Ca\(^{2+}\) pumps could be derived from unrelated protein(s) contaminating the ATPase preparations or from specific sequences present in a different isoform that may also be expressed in erythrocytes. However, the two isoforms reported here correspond in all likelihood to (the) two major calmodulin-binding Ca\(^{2+}\) pumps of human erythrocytes. Moreover, given the purity of the erythrocyte membrane preparations used as the starting material, it is unlikely that one of the two sequences is exclusively derived from a pump isoform expressed only in “contaminating” cells (e.g., lymphocytes or platelets). In addition, probes specific for these two isoforms detect major large mRNAs on Northern blots of erythroid RNA derived from human K562 cells. It remains to be determined, however, whether both isoforms are co-expressed in the same erythrocyte, and whether functional differences exist between these isoforms. This last point is discussed in more detail below.

**Possible Functional Differences between Calcium Pump Isoforms**—It has been shown previously that the Ca\(^{2+}\)-dependent ATPase activity of the purified human erythrocyte Ca\(^{2+}\) pump can be stimulated by phosphorylation via the cAMP-dependent kinase (Caroni and Carafoli, 1981; Neyes et al., 1985; James et al., 1989). However, even under the most favorable in vitro conditions the stoichiometry of the phosphorylation does not exceed 0.7 phosphate molecules incorporated per ATPase molecule, indicating that a maximum of about 70% of the erythrocyte ATPase molecules can be phosphorylated. Since at least two different Ca\(^{2+}\) pump isoforms are expressed in erythrocyte membranes, this result could be explained by the presence of two isoforms differing in susceptibility towards cAMP-dependent phosphorylation. In contrast to the previously reported pump sequence, the novel isoform described here indeed lacks a canonical sequence for phosphorylation by the cAMP kinase in the COOH-terminal regulatory region. Direct sequencing of the erythrocyte Ca\(^{2+}\) pump labeled upon phosphorylation by the cAMP kinase has resulted in the identification of a serine residue (Ser\(_{u7}\)) as the phosphorylation target (James et al., 1989). This residue was embedded in a sequence that matches the predicted sequence found only in the hPMCA1b isoform. Whether the sequence DKAS, identified in the hPMCA3 isoform about 15 residues “upstream” of the phosphorylation site in the hPMCA1b protein (see “Results”), can act as an alternative phosphorylation substrate cannot be decided at the moment. Final proof of functional differences between the two human erythrocyte Ca\(^{2+}\) pump isoforms must necessarily await studies on purified proteins separately expressed from their respective cDNA. However, the data discussed here indicate that the two isoforms may differ in their mode of regulation.

The regions of remarkable sequence divergence in the two isoforms are of particular interest to test models of the structure and function of the plasma membrane Ca\(^{2+}\) pump. For example, the region just NH\(_2\)-terminal to the second putative transmembrane domain (comprising residues 120–150 and 119–145, respectively, in the two isoforms) is highly divergent. Assuming that this region is located extracellularly (Verma et al., 1988) it may contribute significantly to the specific antigenicity of a given isoform. The divergence in this region could thus allow the production of isoform-specific antibodies useful in immunohistochemical studies of isoform tissue distribution.

The region encompassing residues 293–317 and 289–307, respectively, is also divergent in the two isoforms, not only in terms of actual sequence but also with respect to its length. It represents one of the most highly charged regions in the pump sequence and residues 310–321 (of the first isoform) display some similarity with an “E-F-hand” loop sequence. A possible participation of this region (“Domain D” in Verma et al., 1988) in Ca\(^{2+}\) binding has been cautiously suggested. Considering the striking divergence between the two isoforms in this region its role as an essential Ca\(^{2+}\) binding or transport domain appears unlikely. The second region proposed as a possible Ca\(^{2+}\) binding site (Domain A in Verma et al., 1988), comprising residues 1079–1099 and 1067–1085, respectively, in the two known human pump isoforms is also of interest. This negatively charged domain differs in length in the two isoforms, the novel sequence being shorter by 2 residues. This region is located on the NH\(_{2}\)-terminal side of the well-conserved calmodulin-binding site and it has been proposed that it might form a negatively charged α-helical domain involved in Ca\(^{2+}\) binding. The latter would occur when the positively charged calmodulin-binding domain is released from the acidic sequence upon binding of calmodulin (Verma et al., 1988; Strehler and Carafoli, 1968; Carafoli et al., 1989). If this putative Ca\(^{2+}\)-binding domain indeed assumes a helical conformation in vivo, a deletion of 2 residues would correspond to a shift by about two-thirds of a turn. This could conceivably influence the Ca\(^{2+}\)-binding and calmodulin-activation properties of the corresponding isoforms. The entire COOH-terminal regulatory region, which differs so significantly in the two isoforms, is now in principle amenable to detailed structure-function studies. Its expression from the corresponding cDNA for each isoform, as well as site-directed mutagenesis to alter specific residues, are promising tools to shed light on these questions.

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Note Added in Proof—While this paper was in press, Shull and Greeb (1989) reported the cDNA-deduced sequence of a novel rat PMCA isoform which they termed PMCA3. Since this isoform does not correspond to the novel human isoform hPMCA3 described in this contribution, the human enzyme described here should henceforth be called hPMCA4 to avoid confusion and to maintain consistency in the terminology.

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