Cloning of a cDNA for the Human Cell Adhesion Kinase β

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ABSTRACT

Cell adhesion kinase β (CAKβ) is the second protein-tyrosine kinase (PTK) of the focal adhesion kinase (FAK) subfamily with large N- and C-domains in addition to the central kinase domain but without Src homology 2 and 3 (SH-2 and SH-3) domains. In this paper, cloning and sequencing of a cDNA encoding human CAKβ are described. A full-length clone (clone B) contained 4,157-base pairs of human CAKβ cDNA including 243-base pairs of the 5'-untranslated sequence and 881-base pairs of the 3'-untranslated sequence with a polyadenylation signal (ATTAAA). The clone B of human CAKβ cDNA has an open reading frame encoding 1009 amino acid residues; the human CAKβ has the same number of amino acid residues in the N-, C-, and kinase-domains as rat CAKβ. The amino acid sequence of human CAKβ is 95.4% identical with that of rat CAKβ. The species difference is most prominent in the C-domain. All three previously-recognized, subfamily-specific residues in the kinase domains of FAK and the rat CAKβ are also found in the human CAKβ. The residues V^{552} and A^{612}, which have been considered to be characteristic to CAKβ, are found to be conserved also in the human CAKβ. It has been postulated that CAKβ is important as a docking protein. The autophosphorylation site and also the ligand site to the SH-2 domains of the Src-family PTKs, Y^{402}AEI, are found to be conserved in the human CAKβ. The ligand sequence for the Grb2 SH-2 domain, Y^{881}HNV of the rat CAKβ, is found functionally conserved in the human CAKβ, Y^{881}LNV. The third ligand sequence, E^{712}PPPKPSR, participating in the binding to the SH-3 domains of pp130^{cas} and Efs, is also found conserved in the human CAKβ. The extreme N-terminal 88 amino acid residues of the rat CAKβ were previously found entirely different from FAK and found unique to CAKβ. Ninety four percent of those 88 residues in the human CAKβ are found identical with the rat CAKβ. This high sequence homology strongly suggests

Abbreviations:
PTK, protein-tyrosine kinase FAK, focal adhesion kinase CAKβ, cell adhesion kinase β
SH-2, Src homology 2 SH-3, Src homology 3.

that this region is involved in the specific function of CAKβ different from FAK.

Key words: Cell adhesion kinase β (CAKβ), Focal adhesion kinase (FAK), Autophosphorylation site, Src homology 2 and 3 (SH-2 and SH-3) domains.

INTRODUCTION

The protein-tyrosine kinases (PTKs) that do not span the plasma membrane (the so-called nonreceptor PTKs) have been classified into different subclasses (subfamilies) based on sequence similarities and distinct structural characteristics (1). Cell adhesion kinase β (CAKβ) is the second PTK of the focal adhesion kinase (FAK) subfamily (2), with large N- and C-domains in addition to the central kinase domain but without Src homology 2 and 3 (SH-2 and SH-3) domains. The cDNAs of the protein have been cloned from a rat and a human by us (2) and from a human by Lev *et al.* (3); these results were published almost at the same time. In the following two months, the cloning of CAKβ was also reported by two other groups of researchers (4, 5). CAKβ has been named PYK2 (3), RAFTK (4), and FAK2 (5) by these other groups. The expression of the protein is high in brain, intestine, kidney, spleen and lung (2); the CAKβ gene is less evenly expressed in a variety of organs than the FAK gene. It has been reported (3) that CAKβ is activated on elevation of cytoplasmic free Ca^{2+} concentration and its participation in neural plasticity is postulated (6). However, the signaling pathways where CAKβ functions remain largely to be elucidated in the future. CAKβ has at least three characteristic ligand sequences in common with FAK. The first one is the autophosphorylation site (residues 402-405), which participates in binding to the SH-2 domains of the Src-family kinases. The second one is the ligand sequence to the SH-3 domains of $pp130^{cas}$ and Efs (7, 8) (residues 712-719). The third one works as the ligand to the SH-2 domain of Grb2 (9) on phosphorylation (residues 881-884).

In this paper, we describe the cloning and sequencing of a cDNA encoding human CAKβ. A full-length clone (clone B) covering 243 base pairs of 5'-untranslated sequence, all coding sequence, and 3'-untranslated sequence with a polyadenylation signal was isolated from a human hippocampus cDNA library.

MATERIALS AND METHODS

Isolation of cDNA clones encoding human CAKβ and determination of nucleotide sequence

Rat CAKβ cDNA fragments corresponding to the amino acid residues 81-319

[α-^{32}P] dCTP (Amersham) using a random primer labeling system (BcaBEST labeling kit, Takara Shuzoh). A mixture of the labeled probes was used to screen an oligo(dT)- and random-primed human (normal female, 2 years old) hippocampus cDNA library constructed in λZAPII vector (Stratagene, catalog No. 936205). Two positive phage plaques (clones A and B) were identified. The nucleotide sequence of clone B was determined by the dideoxynucleotide chain termination method (10) using the BcaBEST dideoxy sequencing kit (Takara Shuzo, Otsu, Japan). The sequence of both strands was determined for the derivatives of clone B, prepared by exonuclease III/Mung Bean nuclease deletions.

RESULTS AND DISCUSSION

The human CAKβ cDNA was isolated by screening a human hippocampus cDNA library in λZAPII vector with a mixture of rat CAKβ cDNA fragments corresponding to the amino acid residues 81-319 and 735-1008 as probes. The cDNA fragments corresponding to the N- and C-domains but not the kinase-domain were chosen as specific probes for CAKβ cDNA. Two positive phage plaques were identified. One clone (clone A) contained a human CAKβ cDNA starting from the sequence corresponding to the base number 1827 (amino acid residue 523) of rat CAKβ cDNA ending at the poly (A) tail. The other (clone B) contained a 4.15-kilobase human CAKβ cDNA from the 5'-untranslated sequence to the 3'-untranslated sequence with a polyadenylation signal (ATTAAA) but without a poly (A) tail (Fig. 1). The nucleotide sequence of clone B has been submitted to the NCBI (GenBank) nucleotide sequence data base with the accession No. U43522.

The clone B of human CAKβ cDNA contained an open reading frame encoding 1009 amino acid residues, a flanking 5'-untranslated sequence of 243 base pairs, and a 3'-untranslated sequence of 881 base pairs (Fig. 1). The human CAKβ has the same number of amino acid residues in the N-, C-, and kinase-domains as rat CAKβ (2) (Fig. 2). The amino acid sequence of the human CAKβ is 95.4% identical with that of the rat CAKβ (Fig. 2). The amino acid sequences of the rat and mouse CAKβs are 98.4% identical (the mouse CAKβ sequence was taken from Avraham *et al.* (4)) (Fig. 2). These species differences are most prominent in the C-domain; the percentage of identical amino acid residues in the kinase-, N-, and C-domains of human and rat CAKβs are 97.7%, 96.7%, and 92.1%, respectively. In addition to our human CAKβ cDNA sequence, three other human CAKβ cDNA sequences have been reported (3, 4 and GenBank L49207 (5)); two of the cDNAs, the proteins encoded in which are named PYK2 (3) and FAK2 (5), were cloned from cDNA libraries

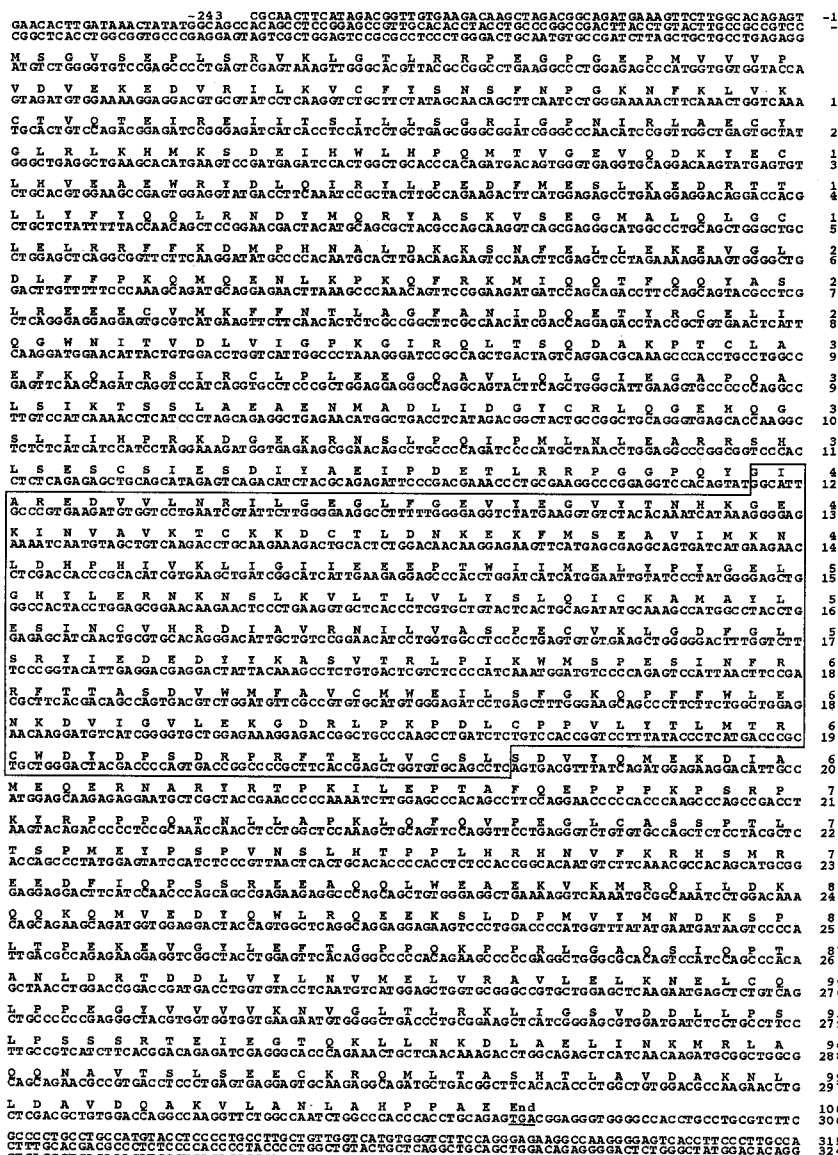
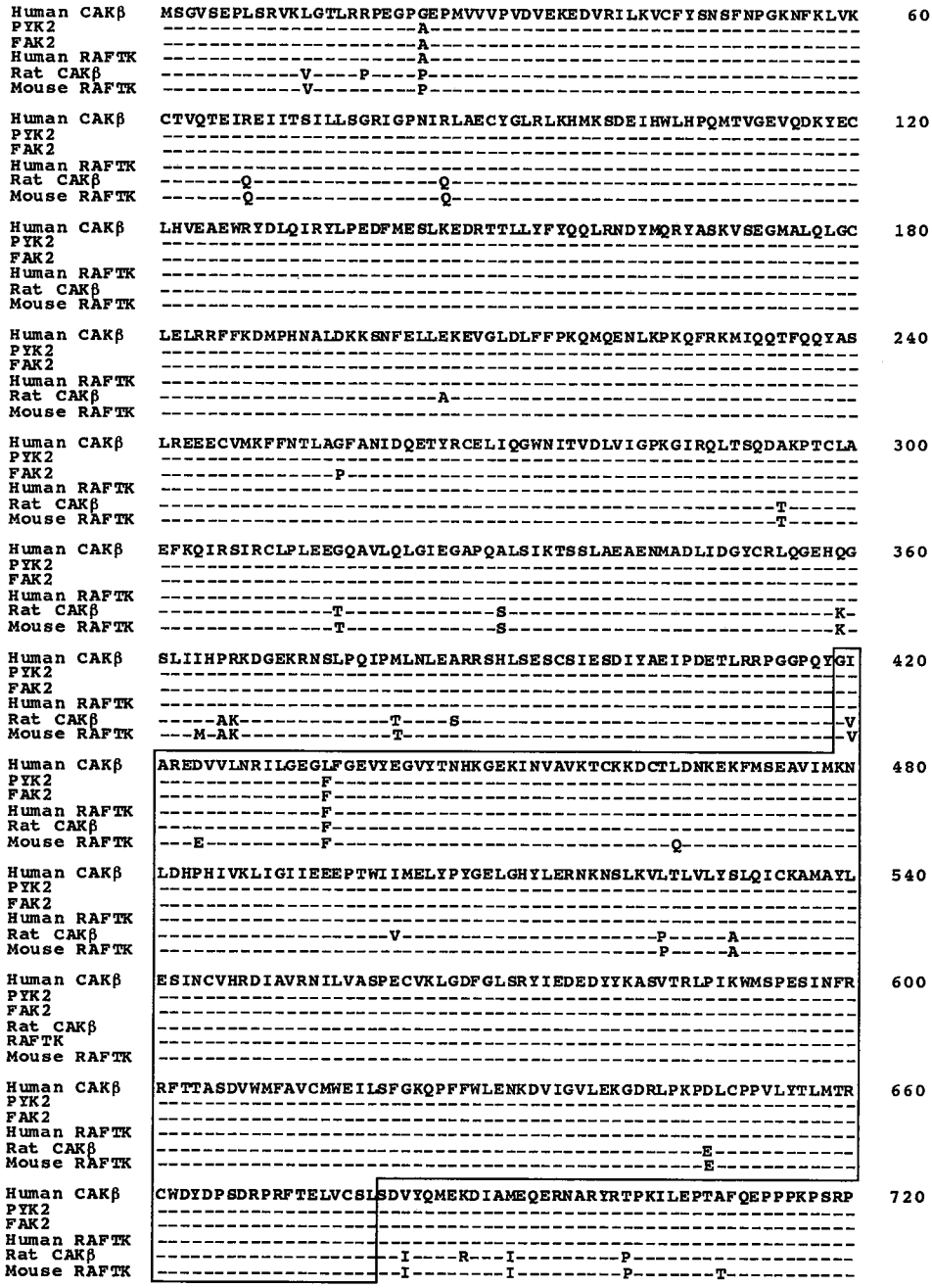


Fig. 1 Nucleotide sequence of human CAKβ cDNA (clone B) and deduced amino acid sequence. Nucleotides and corresponding amino acids (single-letter code) shown above are *numbered* at the end of each lane. The catalytic domain of the PTK is indicated by a *box*. The translational stop codon is *underlined*. A variation of the polyadenylation signal, ATTAAA, near the 3'-end of the cDNA, is also *underlined*.


Human CAKβ MSGVSEPLSRVKLGTLRRPEGPGEPMVVVPVDVEKEDVRILKVCFYSNSFNPGKNFKLVK 60
PYK2 ----------A----------
FAK2 ----------A----------
Human RAFTK ----------A----------
Rat CAKβ ----------V----P----P----------
Mouse RAFTK ----------V---------P----------
Human CAKβ CTVQTEIREIITSILLSGRIGPNIRLAECYGLRLKHMKSDEIHWLHPQMTVGEVQDKYEC 120
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ -------Q----------Q----------
Mouse RAFTK -------Q----------Q----------
Human CAKβ LHVEAEWRYDLQIRYLPEDFMESLKEDRTTLLYFYQQLRNDYMQRYASKVSEGMALQLGC 180
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------
Mouse RAFTK ----------
Human CAKβ LELRRFFKDMPHNALDKKSNFELLEKEVGLDLFFPKQMQENLKPKQFRKMIQQTFQQYAS 240
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------A----------
Mouse RAFTK ----------
Human CAKβ LREEECVMKFFNTLAGFANIDQETYRCELIQGWNITVDLVIGPKGIRQLTSQDAKPTCLA 300
PYK2 ----------
FAK2 ----------P----------
Human RAFTK ----------
Rat CAKβ ----------T------
Mouse RAFTK ----------T------
Human CAKβ EFKQIRSIRCLPLEEGQAVLQLGIEGAPQALSIKTSSLAEAENMADLIDGYCRLQGEHQG 360
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------T----------S----------K-
Mouse RAFTK ----------T----------S----------K-
Human CAKβ SLIIHPRKDGEKRNSLPQIPMLNLEARRSHLSESCSIESDIYAEIPDETLRRPGGPQYGI 420
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ -----AK----------T----S----------V
Mouse RAFTK ---M-AK----------T----------V
Human CAKβ ARDVVLNRILGEGLFGEVYEGVYTNHKGEKINVAVKTCKKDCTLDNKEKFMSEAVIMKN 480
PYK2 ----------F----------
FAK2 ----------F----------
Human RAFTK ----------F----------
Rat CAKβ ----------F----------
Mouse RAFTK ---E----------F----------Q----------
Human CAKβ LDHPHIVKLIGIIEEEPTWIIMELYPYGELGHYLERNKNSLKVLTLVLYSLQICKAMAYL 540
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------V----------P-----A----------
Mouse RAFTK ----------P-----A----------
Human CAKβ ESINCVHRDIAVRNILVASPECVKLGDFGLSRYIEDEDYYKASVTRLPIKWMSPESINFR 600
PYK2 ----------
FAK2 ----------
Rat CAKβ ----------
RAFTK ----------
Mouse RAFTK ----------
Human CAKβ RFTTASDVWMFAVCMWEILSFGKQPFFWLENKDVIGVLEKGDRLPKPDLCPPVLYTLMTR 660
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------E----------
Mouse RAFTK ----------E----------
Human CAKβ CWDYDPSDRPRFTELVCSLSDVYQMEKDIAMEQERNARYRTPKILEPTAFQEPPPKPSRP 720
PYK2 ----------
FAK2 ----------
Human RAFTK ----------
Rat CAKβ ----------I----R---I---------P----------
Mouse RAFTK ----------I---------I---------P-------T----------

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Human CAKβ   KYRPPPQTNLLAPKLQFQVPEGLCASSPTLTSPMEYPSPVNSLHTPPLHRHNVFKRHSMR   780
PYK2         ------------------------------------------------------------
FAK2         ------------------------------------------------------------G
Human RAFTK  ------------------------------------------------------------
Rat CAKβ     --KH--------------------------------------------------------
Mouse RAFTK  ------------------------------------------------------------

Human CAKβ   EEDFIQPSSREEAQQLWEAEKVKMRQILDKQQKQMVEDYQWLRQEEKSLDPMVYMNDKSP   840
PYK2         ------------------------------------------------------------
FAK2         ------------------------------------------------------------
Human RAFTK  ------------------------------------------------------------
Rat CAKβ     -----R---------------I----V--R--------S----R--RC-------------
Mouse RAFTK  -----R---------------I--K-V-ER--------S----R--RC-------------

Human CAKβ   LTPEKEVGYLEFTGPPQKPPRLGAQSIQPTANLDRTDDLVYLNVMELVRAVLELKNELCQ   900
PYK2         ------------------------------------------------------------
FAK2         ------------------------------------------------------------
Human RAFTK  ------------------------------------------------------------
Rat CAKβ     ------A--T--------------------------------H---T--E-------K-S-
Mouse RAFTK  ------A--T--------------------------------H---T--E-------K-G-

Human CAKβ   LPPEGYVVVVKNVGLTLRKLIGSVDDLLPSLPSSSRTEIEGTQKLLNKDLAELINKMRLA   960
PYK2         ------------------------------------------------------------
FAK2         ------------------------------------------------------------
Human RAFTK  ------------------------------------------------------------
Rat CAKβ     ----E----------N---------------A-------------------------
Mouse RAFTK  ----D----------N---------------A----------------------K--

Human CAKβ   QQNAVTSLSEECKRQMLTASHTLAVDAKNLLDAVDQAKVLANLAHPPAE          1009
PYK2         ---------------------------------------------
FAK2         ---------------------------------------------
Human RAFTK  ---------------------------------------------
Rat CAKβ     ----------D-------------------------V---------
Mouse RAFTK  ----------D-------------------------V---------
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Fig. 2 Comparison of amino acid sequences of human, rat, and mouse CAKβs. The catalytic domains are *boxed*. Identical residues to human CAKβ in the 2nd-4th human sequences and in the rat CAKβ and mouse RAFTK are indicated by *dashes*. The sequences used in the alignments were taken from the references indicated: PYK2(3), FAK2(5), human and mouse RAFTK(4), and rat CAKβ(2).

prepared either from a human fetal brain (3) or from an adult male hippocampus (5); the other one, whose protein is named RAFTK (4), was cloned from the same cDNA library as we used. These four sequences are different only in 3 amino acid residues (Fig. 2), but their 5'- and 3'-untranslated sequences are significantly different (Figs. 3 and 4). The cDNA clones encoding RAFTK, CAKβ, FAK2, and PYK2 have 5'-untranslated sequences of 293-, 243-, 180-, and 107-base pairs, respectively; each of these has a unique extreme 5'-terminal sequence of 7-120 base pairs (Fig. 3). The cDNA clones encoding FAK2, CAKβ, RAFTK, and PYK2 have 3'-untranslated sequences of 882-, 881-, 301-, and 281-base pairs, respectively; only the 3'-untranslated sequences of the cDNA clones encoding CAKβ and FAK2 extend to the polyadenylation signal (Fig. 4).

FAK and rat CAKβ have several characteristic residues in common in the kinase domains (2). All these previously-recognized, subfamily-specific residues, A^{536}, I^{550}, and F^{626}, are found conserved in the human and mouse CAKβs (Fig. 2). The residues V^{552} and A^{612} have been recognized as the residues characteristic to CAKβ, not commonly found in other PTKs including FAK (2). They are also found conserved in the human and mouse CAKβs (Fig. 2).

```
CAKβ                                                          -243  CGC  -241
RAFTK    -293  AACCACAAGTCAAATAGAAAGAAGTTAAAAGAATGTTTATGCAAACACATGAG

CAKβ     AACTTCATAGACGGTTGTGAAGACAAGCTAGACGGCAGATGAAAGTTCTTGGCACAGAGT  -181
RAFTK    AAAAGAAGGGTGCAGATGAGAATAGGGGTGTGGTTAACAACTCAGAGGAGGAGGGAGAAT

CAKβ     GAACACTTGATAAACTATATGGCAGCCACAGCCTCCGGAGCCGTTGCACACCTACCTGCC  -121
FAK2     GAATTCCGTCAGCCCTTTTACT----------------------------------------
RAFTK    CTAACCTGTCAGCCCTTTTACT----------------------------------------

CAKβ     CGGCCGACTTACCTGTACTTGCCGCCGTCCCGGCTCACCTGGCGGTGCCCGAGGAGTAGT   -61
PYK2           -107  CGGTACAGGTAAGTCGGCCGGGCAGGTAGG-----------------
FAK2     ----------------------------------------------------------
RAFTK    ----------------------------------------------------------

CAKβ     CGCTGGAGTCCGCGCCTCCCTGGGACTGCAATGTGCCGATCTTAGCTGCTGCCTGAGAGG    -1
PYK2     ---------------------------------------G--------------------
FAK2     ----------------------------------------------------------
RAFTK    ----------------------------------------------------------
```

Fig. 3 Comparison of nucleotide sequences of the 5'-untranslated portions of human CAKβ cDNA and human cDNAs encoding the same protein as CAKβ. The sequences used in the alignments were taken from the references indicated: PYK2(3), FAK2(5), and RAFTK(4).

It has been shown that paxillin and talin bind to the C-terminal domain of FAK (11, 12). The postulated FAK sequence important in the paxillin binding (11) is partly but not completely conserved in CAKβ. We have observed that paxillin coprecipitates to some extent with CAKβ when the immunoprecipitates from brain- and WFB cell-lysates with anti-CAKβ, directed against amino acid residues 670-716, were analyzed (unpublished.). Further experiments are required to clarify whether CAKβ binds directly to paxillin or not.

In addition to its specific binding to paxillin and talin, FAK is important as a docking protein. Three regions of the FAK sequence have so far been identified as the ligand sequences (13). All these ligand sequences were found conserved in CAKβ. The tyrosine residue of FAK corresponding to the residue 402 of CAKβ is known to be the site of autophosphorylation and also the ligand site to which the Src-family PTKs bind by their SH-2 domains resulting in their activation. The consensus amino acid sequence for this Src SH-2 binding found in FAK, YAEI, and the preceding acidic residues are conserved in the human, rat, and mouse CAKβ sequences (Fig. 2). The second FAK sequence for a SH-2 binding corresponds to the residue 881-884, YHNV, of the rat CAKβ, which is the ligand site for Grb2 (9). The consensus ligand sequence for this Grb2 SH-2 binding, Y^{925}ENV of the mouse FAK, is also found functionally conserved in the human, rat, and mouse CAKβs: Y^{881}HNV of the rat CAKβ and Y^{881}LNV of the human CAKβ (Fig. 2). The third ligand sequence in FAK participates in the

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CAKβ   TGACGGAGGGTGGGG.CCACCTGCCTGCGTCTTC.GCCCCTGCCTGCCATGTACCTCCCC   58
PYK2   ---------------G-----------------C-------------------------   60
FAK2   ---------------G-----------------C-------------------------   60
RAFTK  ---------------G-----------------C-------------------------   60

CAKβ   TGCCTTGCTGTTGGTCATGTGGGTCTTCCAGGGAGAAGGCCAAGGGGAGTCACCTTCCCT  118
PYK2   ------------------------------------------------------------  120
FAK2   ------------------------------------------------------------  120
RAFTK  ------------------------------------------------------------  120

CAKβ   TGCCACTTTGCACGACGCCCTCTCCCCACCCCTACCCCTGGCTGTACTGCTCAGGCTGCA  178
PYK2   ------------------------------------------------------------  180
FAK2   ------------------------------------------------------------  180
RAFTK  ------------------------------------------TG----------------  180

CAKβ   GCTGGACAGAGGGGACTCTGGGCTATGGACACAGGGTGACGGTGACAAAGATGGCTCAGA  238
PYK2   ------------------------------------------------------------  240
FAK2   ------------------------------------------------------------  240
RAFTK  ------------------------------------------------------------  240

CAKβ   GGGGGACTGCTGCTGCCTGGCCACTGCTCCCTAAGCCAGCCTGGTCCATGCAGGGGGCTC  298
PYK2   ------------------------------------------  281
FAK2   ------------------------------------------------------------  300
RAFTK  ------------------------------------------------------------  300

CAKβ   CTGGGGGTGGGGAGGTGTCACATGGTGCCCCTAGCTTTATATATGGACATGGCAGGCCGA  358
FAK2   ------------------------------------------------------------  360
RAFTK  G  301

CAKβ   TTTGGGAACCAAGCTATTCCTTTCCCTTCCTCTTCGGCCCTCAGATGTCCCTTGATGCAC  418
FAK2   ----------------------------------TC------------------------  420

CAKβ   AGAGAAGCTGGGGAGGAGCTTTGTTTT.GGGGGTCAGGCAGCCAGTGAGATGAGGGATGG  477
FAK2   --------------------------C---------------------------------  480

CAKβ   GCCTGGCATTCTTGTACAGTGTATATTGAAATTTATTTAATGTGAG.TTTGGTCTGGACT  536
FAK2   ------------------------------------------------G-------------  540

CAKβ   GACAGCATGTGCCCTCCTGAGGGAGGACCTGGGGCACAGTCCAGGAACAAGCTAATTGGG  596
FAK2   ----------------------------A---.-------------------------  599

CAKβ   AGTCCAGGCACAGGATGCTGTGTTGTCAACAAACCAAGCATCAGGGGGAAGAAGCAGAGA  656
FAK2   ------------------------------------------------------------  659

CAKβ   GATGCGGCCAAGATAGGACCTTGGGCCAAATCCGCTCTCTTCCTGCCCCTCTTTCTCTTT  716
FAK2   ------------------------------------------------------------  719

CAKβ   CTTCCTTTACTTTCCCTTGCTTTTCCCTCTTTTCTTACTCCTCCTCTTTCTCTCCCCAAC  776
FAK2   ------------------------------------------------------C--  779

CAKβ   CCCCATTCTCATCTGCACCCTTCTTTTCTCATGTGTTTGCATAAACATTCTTTTAACTTC  836
FAK2   ------------------------------------------------------------  839

CAKβ   TTTCTATTTGACTTGTGGTTGAATTAAAATTGTCCCATTTGCTTG   881
FAK2   ----------------------------------------A   882
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Fig. 4 Comparison of nucleotide sequences of the 3'-untranslated portions of human CAKβ cDNA and human cDNAs encoding the same protein as CAKβ. The sequences used in the alignments were taken from the references indicated: PYK2 (3), FAK2 (5), and RAFTK (4).

binding to the SH-3 domains of pp130^{cas} and Efs (7, 8). This ligand sequence in FAK, EAPPKPSR, is functionally conserved in the human, rat, and mouse CAKβs and corresponds to the residues 712-719, EPPPKPSR, of CAKβ (Fig. 2). The binding of pp130^{cas} and Efs to CAKβ has been shown by the coimmunoprecipitation of pp130^{cas} and Efs with CAKβ and by the specific binding of Efs to a GST-fusion protein of the CAKβ C-domain residue 670-792 (our unpublished observation).

There is one more proline-rich sequence in the N-terminal region of the rat CAKβ, PPEGPPEP of the residues 18-25 (2). The positioning of prolines in this sequence indicates that the sequence cannot fold into a polyproline type 2 helix structure, which is essential as a ligand for a SH-3 domain. The corresponding region in the human CAKβ is not proline-rich as a result of the replacement of two proline residues with other amino acids (Fig. 2), which confirms the deduction on the function of this region described above.

It has been shown that the extreme N-terminal 88 residues of the rat CAKβ is entirely different from any portion of FAK (2). 94.3% and 98.9% of the amino acid residues in this stretch of the human and mouse CAKβs, respectively, are identical with those of the rat CAKβ. The high sequence homology in these 88 residues of the rat, human, and mouse CAKβs strongly suggests that this region is involved in a specific function of CAKβ different from FAK. One obvious possibility how this extreme N-terminal region of CAKβ participates in the CAKβ-specific process is the recognition and binding of a unique transmembrane receptor by this N-terminal region. It has been shown that FAK binds the cytoplasmic region of β-integrins by its N- domain.

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