Caspases Cleave Focal Adhesion Kinase during Apoptosis to Generate a FRNK-like Polypeptide*

(Received for publication, February 17, 1998)

François G. Gervais‡, Nancy A. Thornberry§, Salvatore C. Ruffolo‡, Donald W. Nicholson‡, and Sophie Roy¶

From the ‡Department of Biochemistry and Molecular Biology, Merck Frosst Centre for Therapeutic Research, Pointe Claire-Dorval, Quebec H9R 4P8, Canada and the §Department of Enzymology, Merck Research Laboratories, Rahway, New Jersey 07065

Focal adhesion kinase (Fak) is a non-receptor protein-tyrosine kinase that stimulates cell spreading and motility by promoting the formation of contact sites between the cell and the extracellular matrix (focal adhesions). It suppresses apoptosis by transducing survival signals that emanate from focal adhesions via the clustering of transmembrane integrins by components of the extracellular matrix. We demonstrate that Fak is cleaved by caspases at two distinct sites during apoptosis. The sites were mapped to DQTD772, which was preferentially cleaved by caspase-3, and VSWD704, which was preferentially cleaved by caspase-6 and cytotoxic T lymphocyte-derived granzyme B. The cleavage of Fak during apoptosis separates the tyrosine kinase domain from the focal adhesion targeting (FAT) domain. The carboxyl-terminal fragments that are generated suppress phosphorylation of endogenous Fak and thus resemble a natural variant of Fak, FRNK, that inhibits Fak activity by preventing the localization of Fak to focal adhesions. The cleavage of Fak by caspases may thus play an important role in the execution of the suicide program by disabling the anti-apoptotic function of Fak. Interestingly, rodent Fak lacks an optimal caspase-3 consensus cleavage site although it is cleaved in murine cells undergoing apoptosis at an upstream site. This appears to be the first example of a caspase substrate where the cleavage sites are not conserved between species.

Fak is a 125-kDa non-receptor protein-tyrosine kinase that is recruited to and activated by the engagement of transmembrane integrins by components of the extracellular matrix (e.g. fibronectin) during integrin-mediated cell adhesion. The activation of Fak leads to (i) activation of the Ras-mitogen-activated protein kinase pathway and (ii) recruitment and phosphorylation (either directly or indirectly via the recruitment of Src-like tyrosine kinases) of a number of cytoskeletal proteins, resulting in the formation of contact sites between the cell surface and the extracellular matrix called focal adhesions. By activating the Ras-mitogen-activated protein kinase pathway and promoting the assembly of focal adhesions, Fak mediates multiple cellular responses to cell adhesion including cell survival and proliferation as well as cell spreading and motility (for review, see Ref. 1). Fak function is dependent on two distinct domains: the tyrosine kinase domain within the amino-terminal half of the protein and the focal adhesion targeting (FAT) domain within the carboxyl-terminal half of the protein. Fak is negatively regulated by the expression of FRNK (p41FRNK), a truncated isoform of Fak that contains a FAT domain but lacks the kinase domain (7). FRNK inhibits the cellular responses to adhesion by preventing the localization of Fak to sites of integrin clustering (8).

The importance of Fak in transducing an anti-apoptotic signal upon integrin engagement is underscored by a number of studies: (i) constitutively activated forms of Fak prevent epithelial cell death upon cell detachment (anoikis) (9); (ii) inhibition of Fak in cultured fibroblasts results in apoptosis (10); (iii) Fak is overexpressed in some types of cancers (11–14); and (iv) antisense oligonucleotides to Fak induce apoptosis in tumor cells (15). It is therefore not surprising that Fak has been shown to be the target of proteolysis in chicken embryo fibroblasts undergoing apoptosis (16). More recently, these observations were extended in human cell lines undergoing apoptosis and the caspase family of cysteine-specific proteases were directly implicated in Fak cleavage (17) and disassembly of focal adhesions (18). The caspases are responsible for initiating and executing apoptotic cell death by cleaving critical homeostatic, repair, and structural proteins in the dying cell (for review see Ref. 19). In this report, we identify two sites within chicken Fak that are cleaved by caspases in vitro and in apoptotic cells. Cleavage at either site results in the separation of the kinase domain from the FAT domain. Fragments containing the FAT domain, when expressed in HeLa cells, inhibit phosphorylation of endogenous Fak, suggesting that they act like FRNK and interfere with the function of uncleaved Fak. Although the molecular masses of the fragments released from the cleavage of human Fak in cells undergoing apoptosis are consistent with the sites identified in chicken Fak, cleavage of murine Fak appears to occur at a different site.

EXPERIMENTAL PROCEDURES

Plasmid Construction and Mutagenesis—The chicken Fak cDNA (in pBluescript II KS−) was the kind gift of Dr. M. Schaller (University of North Carolina). The D772A mutation was made by an overlap extension PCR method (20). The complementary inverse oligonucleotides 5’...
GAT CAA ACA GCC TCC TGG AAC 3' and 5'TTT CCA GGA AGC TCT TTG ATC 3' were used in combination with the internal oligonucleotides 5' AAGCCCTTCTCGGAGG TG 3' and 5' ATGCTGATACCCTCGGAGG TG 3'. From the large PCR fragment, a 417-base pair insert was sequenced to ensure that no other mutation was introduced inadvertently. A similar strategy was used to generate the D704A mutation using the complementary inverse oligonucleotides 5' GTCACTGACCTGATCCGTC GGA GCTGAGTACGAGCAGCTGG 3' and 5' TCTGGAATATGTTGGGCTGAC GTC 3'. The mutated fragment was subcloned into the Fak wild-type sequence using the restriction sites PstI and NotI, and the clone was sequence-verified.

The introduction of a flag epitope (DYKDDDDK) at the carboxyl terminus of Fak was performed by PCR with the following oligonucleotides 5' TGG GGC CTG GAC TGG CTG ATC ATT TTC AG 3' and 5' GAA TTC TAG CAA AAC CAT GTC AGG AGG ATC AGA TGA AGC TC 3'. From the large PCR fragment, a 417-base pair fragment was subcloned into the Fak wild-type sequence using the restriction enzymes NotI and EcoRV into the episomal eukaryotic expression vector pCep4 (21) digested with the restriction enzymes NotI and EcoRV into the episomal eukaryotic expression vector pCep4 (21) digested with the restriction enzymes NotI and EcoRV into the episomal eukaryotic expression vector pCep4 (21) digested with the restriction enzymes NotI and EcoRV. For stable expression of Fak in K562 cells, wild-type and mutant Fak cDNAs were subcloned from the pBluescript II KS− digested with the restriction enzymes NotI and EcoRV into the episomal eukaryotic expression vector pCep4 (21) digested with the restriction enzymes NotI and EcoRV into the episomal eukaryotic expression vector pCep4 (21) digested with the restriction enzymes NotI and EcoRV.
5-fold a 5 × RIPA buffer stock (750 mM NaCl, 5% Nonidet P-40, 2.5% sodium deoxycholate, 0.5% SDS, 500 mM Tris, pH 8.0, 25 mM EDTA). Immunoprecipitation of endogenous Fak protein was carried out with 4 mg of an antibody directed against residues 748–1053 of human p125Fak (Upstate Biotechnology). Immune complexes were collected on protein A-Sepharose beads, washed three times in 1/3 RIPA buffer containing 1 mM sodium orthovanadate, and eluted in Laemmli buffer by boiling.

Tyrosine phosphorylation of endogenous Fak was visualized by SDS–4–20% PAGE, transfer to nitrocellulose, and immunoblotting with the RC20 anti-phosphotyrosine antibody (Transduction Laboratories) using enhanced chemiluminescence (ECL™ system from Amersham Pharmacia Biotech).

RESULTS

Serum deprivation of chicken embryo fibroblasts was shown recently to result in the proteolysis of Fak into fragments of 70–90 kDa (16). To identify the enzyme responsible for the cleavage of Fak during apoptosis, we set up an in vitro assay whereby [35S]methionine-labeled chicken Fak generated by in vitro transcription/translation was incubated with an apoptotic extract derived from Jurkat T lymphocytic cells treated with an antibody to the CD95 (Fas/Apo-1) death receptor (these cells were chosen because their ability to undergo apoptotic cell death has been extensively characterized). Two fragments of 90 and 35 kDa were observed after incubation with apoptotic but not with non-apoptotic cell extracts (Fig. 1, lanes 1 and 2). The protease inhibitor sensitivity profile of Fak cleavage was measured as described in Fig. 2 to determine the kcat/Km value (see "Materials and Methods").

Cleavage of Fak by Caspases

Fig. 2. Fak cleavage is sensitive to Ac-DEVD-CHO and Ac-IETD-CHO but not to Ac-YVAD-CHO. A, apoptotic Jurkat cell extracts were incubated with [35S]methionine-labeled Fak in the presence of the indicated concentrations of tetrapeptide aldehydes. The cleavage reactions were carried out for 1 h at 37 °C and visualized by 10% SDS-PAGE and fluorography. Arrows indicate full-length Fak (p125Fak) and proteolytic fragments generated (p90, p35). B, quantitation of Fak cleavage, assessed by laser densitometric scanning of the 35-kDa proteolytic fragment, is expressed as a percentage of the control to which no drug was added. From this graph, the IC50 values for the various tetrapeptide aldehydes were determined.

Fig. 3. Cleavage of Fak by rh-caspase-3 in vitro. [35S]Methionine-labeled Fak was incubated with various amounts of rh-caspase-3 for 1 h at 37 °C and visualized by 10% SDS-PAGE and fluorography. Arrows indicate full-length Fak (p125Fak) and proteolytic fragments generated (p90, p35). Fak cleavage was measured as described in Fig. 2 to determine the kcat/Km value (see "Materials and Methods").
Caspase-3 is one of the most abundant Group II caspases in apoptotic Jurkat cell extracts. It has been implicated directly in the cleavage of most of the proteins targeted for proteolysis during apoptosis. To assess whether caspase-3 cleaves Fak and whether this cleavage event is of physiological relevance, [35S]methionine-labeled Fak was incubated with various amounts of purified recombinant human (rh) caspase-3. Fragments with molecular masses identical with those generated by the apoptotic Jurkat cell extract were produced when Fak was incubated with rh-caspase-3 (Fig. 3), consistent with the inhibitor studies implicating a Group II caspase such as caspase-3. The \( k_{\text{cat}}/K_m \) for this substrate was \( 3.4 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} \), only slightly less than that for poly(ADP)-ribose polymerase (\( k_{\text{cat}}/K_m = 15.6 \times 10^5 \text{ M}^{-1} \text{ s}^{-1} \); data not shown), the first identified and most extensively characterized substrate of caspase-3 (23, 24).

Analysis of the fragments generated by the cleavage of [35S]cysteine-labeled Fak by rh-caspase-3 revealed the presence of the 90-kDa fragment but the absence of the 35-kDa fragment (data not shown). Because cysteine residues are absent from the carboxyl-terminal portion of Fak, we predicted that the 35-kDa fragment was derived from the carboxyl terminal of Fak. To confirm that the aspartic acid at position 772 was being cleaved in cells undergoing apoptosis, we incubated wild-type and mutant Fak (D772A) into the eukaryotic expression vector pCEP4 and established polyclonal stable K562 lymphoid cell lines expressing these proteins. The proteins were engineered with a Flag-epitope tag at the carboxyl terminus to allow visualization of the carboxyl-terminal fragments released by proteolysis. Large amounts of the wild-type (wt) and D772A mutant proteins were expressed in these stable cell lines, as assessed by immunoblot analysis using a monoclonal antibody to the

volved, we performed the cleavage assays in the presence of three different tetrapeptide aldehydes, each of which preferentially inhibits a caspase subgroup (22). The interpretation of the results was based on the known selectivity of these inhibitors for all 10 human recombinant caspases. Up to 10 \( \mu \text{M} \) Ac-YVAD-CHO did not prevent the generation of the 90- and 35-kDa proteolytic fragments (Fig. 2A, lanes 15-21), excluding the possibility that one of the Group I caspases (caspase-1, -4, -5; Ref. 22) was responsible for cleavage. In contrast, as little as 100 \( \text{nm} \) Ac-DEVD-CHO completely abolished Fak cleavage (lanes 1-7; IC\(_{50} \) 10 nm) whereas Ac-IETD-CHO inhibited Fak cleavage only when present at moderately high concentrations (lanes 8-14; IC\(_{50} \) 200 nm). The only caspase that has an inhibitor specificity consistent with these results is caspase-3, strongly suggesting that this enzyme is responsible for cleaving Fak in apoptotic extracts.

Fig. 4. Identification of caspase cleavage sites in Fak. A, DQTD\(^{772} \) is cleaved by rh-caspase-3. [35S]Methionine-labeled wild-type (lanes 1 and 2) and mutant (D772A) (lanes 3 and 4) Fak were incubated in the presence (+) or absence (−) of 3.2 \( \text{nm} \) rh-caspase-3 for 1 h at 37 °C. Fak cleavage was visualized by 10% SDS-PAGE and fluorography. Arrows indicate full-length Fak (p125\(^{FAK} \)) and cleaved fragments (p80, p35). B, DQTD\(^{772} \) and VSWD\(^{704} \) are cleaved upon induction of apoptosis in K562 cells. Polyclonal populations of lymphoid K562 cells expressing carboxyl-terminal Flag-tagged wild-type (lanes 1 and 2) and mutant (D772A, lanes 3 and 4; D704A/D772A, lanes 5 and 6) Fak were incubated in the presence (+) or absence (−) of camptothecin for 16 h. Lysates prepared by boiling in SDS-Laemmli buffer were analyzed by 10% SDS-PAGE, transferred to nitrocellulose, and immunoblotted using an anti-flag M2 antibody (Kodak). Arrows indicate full-length (p125\(^{FAK} \)) and cleaved (p40 and p35) Flag-tagged Fak.

Fig. 5. Cleavage of Fak by rh-caspase-6 \( \text{in vitro} \). [35S]Methionine-labeled Fak wild-type (lanes 1 and 2) and mutant (D704A, lane 3; D772A, lane 4; D704A/D772A, lane 5) were incubated with 7.7 \( \text{nm} \) rh-caspase-6 for 1 h at 37 °C and visualized by 10% SDS-PAGE and fluorography. Arrows indicate full-length Fak (p125\(^{FAK} \)) and cleaved fragments (p90, p85, and corresponding p35 and p40).
Flag epitope (Fig. 4B, lanes 1 and 3). When the cells were rendered apoptotic by treatment with the topoisomerase inhibitor camptothecin, Fak cleavage occurred, as visualized by the appearance of the Flag-tagged 35-kDa carboxyl-terminal fragment (lane 2). As expected, the 35-kDa fragment was not detected by cells expressing the D772A mutant Fak, confirming that cleavage at Asp772 was responsible for the liberation of the 35-kDa fragment. Instead, low amounts of a fragment of 40 kDa were detected in apoptotic K562 cells expressing the D772A mutant Fak (lane 4). The corresponding 85-kDa fragment was visualized by Western blot analysis of extracts from apoptotic cells expressing a D772A mutant protein with a Flag-epitope tag at the amino terminus (data not shown). We predicted that the potential cleavage site VSVD704 present up-stream of the aspartic acid at position 772 was also being cleaved under these conditions. This was confirmed by the absence of Fak cleavage in camptothecin-treated K562 cells expressing a Fak mutant whereby the aspartic acids at both positions 704 and 772 were mutated to alanines (lanes 5 and 6).

Cleavage assays using recombinant human caspase-3 excluded the possibility that the VSVD704 site was recognized by caspase-3 (Fig. 3). The substrate specificity profile of the caspase family members (22) suggested that VSVD704 represented a good consensus site for the Group III activator caspases and a poor substrate for Group II enzymes such as caspase-3. Although one of the Group III enzymes, caspase-8, did not cleave at VSVD704, caspase-6 cleaved both VSVD704 and DQTD772 (Fig. 5), as determined in vitro using the recombinant human enzyme. Incubation of wild-type [35S]methionine-labeled Fak with caspase-6 generated both 40- and 35-kDa fragments and the corresponding amino-terminal derived 85- and 90-kDa fragments, respectively (lane 2). Substitution of the aspartic acids at positions 704 and 772 for alanines confirmed that the 40- and 35-kDa fragments were generated by cleavage at VSVD704 and DQTD772, respectively (lanes 3-5). The $k_{cat}/K_m$ values for cleavage at VSVD704 and DQTD772 by rh caspase-6 were $6.5 \times 10^4$ M$^{-1}$ s$^{-1}$ and $5.9 \times 10^4$ M$^{-1}$ s$^{-1}$,
respectively. The serine protease granzyme B, which is present in the granules of cytotoxic T lymphocytes and has been shown to have a very similar substrate specificity to that of Group III activator caspases (22), also cleaved these sites with $k_{cat}/K_m$ values similar to those determined for caspase-6 ($k_{cat}/K_m$ for VSWD$^{704} = 3.1 \times 10^4 M^{-1} s^{-1}$; $k_{cat}/K_m$ for DQTD$^{772} = 8.9 \times 10^4 M^{-1} s^{-1}$). Although both caspase-3 and caspase-6 cleave DQTD$^{772}$, it is noteworthy that the catalytic efficiency of caspase-3 for this site is approximately 6 times greater than that of caspase-6, suggesting that caspase-3 (or another Group II effector caspase) is more likely to be the protease responsible for cleavage at this site in vivo.

The physiological significance of the presence of two distinct caspase cleavage sites in Fak was underscored by examining the cleavage of endogenous protein in human cell lines undergoing apoptosis (both DQTD$^{772}$ and VSWD$^{704}$ are conserved in human Fak). Total cell lysates were prepared from Jurkat cells at various times after stimulation of the CD95 (Fas/Apo-1) death receptor by antibodies to CD95 (Fas/Apo-1) (Fig. 6A). As early as 2 h after the addition of anti-CD95 (Fas/Apo-1), Fak cleavage to a 90-kDa fragment was detected by Western blot analysis using two different antibodies to Fak, one directed against residues 748 to 1053 (a $\alpha$748–1053 and one directed against residues 354–533 (a $\alpha$354–533). The antibody raised against residues 354–533 recognized an additional fragment of 85 kDa. These results are consistent with the cleavage of Fak at both VSWD$^{704}$ and DQTD$^{772}$ sites in apoptotic Jurkat cells (see Fig. 6C). Curiously, only the 90-kDa fragment was generated in the human cervical carcinoma cell line HeLa in response to treatment for 2 h with staurosporine, a nonspecific kinase inhibitor that induces apoptosis (Fig. 6D). A similar result was obtained when we induced apoptosis by serum starvation or by treatment with camptothecin (data not shown). We confirmed that only DQTD$^{772}$ is recognized in apoptotic HeLa cells by demonstrating that cleavage of transiently transfected chicken Fak was abolished when the P1' aspartic acid at position 772 was substituted for alanine without appearance of fragments corresponding to cleavage at VSWD$^{704}$ (data not shown). The absence of cleavage at VSWD$^{704}$ may be due to the absence of caspase-6 (or another caspase capable of cleaving VSWD$^{704}$) or to the inaccessibility of VSWD$^{704}$ in HeLa cells.

Cleavage at either DQTD$^{772}$ or VSWD$^{704}$ results in the separation of the kinase domain from the focal adhesion targeting (FAT) domain. Noteworthy is the fact that the naturally occurring inhibitor of Fak, FRNK, corresponds to the carboxyl-terminal half of Fak, as illustrated in Fig. 6D. When overexpressed, FRNK prevents the localization of Fak to sites of integrin engagement resulting in decreased Fak phosphorylation and inhibition of Fak-mediated cellular responses to cell adhesion (25). In view of the presence of an intact FAT domain within the 35- and 40-kDa fragments generated by caspase cleavage of Fak during apoptosis, we reasoned that these fragments may also act as competitive inhibitors of Fak. To test this hypothesis, Fak deletion mutants identical with the carboxyl-terminal fragments generated during apoptosis were engineered and transiently transfected into HeLa cells. The levels of phosphorylated Fak protein were measured by immunoprecipitation with an anti-Fak antibody and immunoblotting with an anti-phosphotyrosine antibody 24 h after transfection (Fig. 7). Expression of either the 35- (lane 4) or the 40-kDa fragment (lane 3) suppressed the phosphorylation of endogenous Fak, as was observed after transfection of FRNK (lane 2). Like FRNK, these fragments acted as competitive inhibitors because their inhibitory effects were abrogated by overexpressing full-length Fak protein (data not shown).

If the disabling of Fak by caspase cleavage represents a critical step in the execution of the apoptotic program, the two cleavage sites identified should be conserved in other species. Whereas the caspase-6 cleavage site VSWD$^{704}$ is present in all species examined (human, rat, mouse, chicken, frog; Fig. 8), the caspase-3 cleavage site DQTD$^{772}$ is present in chicken and human but not rat or mouse (Fig. 8; the DHMD$^{772}$ sequence present in frog Fak is predicted to be cleaved efficiently by a Group II effector caspase). Given that one of the caspase cleavage sites (DQTD$^{772}$) is absent in mouse Fak, we examined whether Fak cleavage occurred in murine cells in response to an apoptotic stimulus. Lysates were prepared from staurosporine-treated 3T3 L1 fibroblasts and analyzed by immunoblot-
Cleavage of Fak by Caspases

The cleavage of Fak observed in both adherent and suspension cell lines in response to various apoptotic inducers suggests that this proteolytic event plays an important role in the execution of the suicide pathway. Preliminary results by Wen et al. (17) and Levkau et al. (18) demonstrated recently the cleavage of Fak by caspases during apoptosis. We have identified two caspase cleavage sites within the carboxyl-terminal half of Fak. DQTD772, which is preferentially cleaved by the group II effector caspase, caspase-3, and VSVD704, which is preferentially cleaved by the group III activator caspase, caspase-6. Although caspase-3 does not recognize VSVD704, caspase-6 cleaves both DQTD772 and VSVD704 with virtually identical kinetics ($k_{cat}/K_m = 5.9 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$ and $6.5 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$, respectively). The relative promiscuity of caspase-6 versus caspase-3 is consistent with results obtained from a combinatorial tetrapeptide library used to define the substrate specificity of the caspase family members (22). This combinatorial approach revealed that in the critical specificity-determining P$_3$ subsite, caspase-6 tolerates a number of amino acids whereas caspase-3 exhibits a very strict requirement for aspartic acid.

Our studies underscore the importance of determining the catalytic efficiency of cleavage for a given substrate with a given caspase. Indeed, although caspase-6 can cleave DQTD772 ($k_{cat}/K_m = 5.9 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$), this site is clearly preferred by caspase-3 ($k_{cat}/K_m = 3.4 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$). Of interest is our observation that whereas DQTD772 is cleaved in all human cell lines examined, presumably because Group II effector caspases are present in these cell lines, cleavage at VSVD704 appears to be cell type-dependent, possibly because Group III activator caspases capable of cleaving this site are not ubiquitously expressed. It is of interest that the caspase cleavage sites lie on either side of a proline-rich region shown to interact with two SH3-containing proteins: Graf (a Rho and Cdc42 GTPase-activating protein; Ref. 26) and p130Cas (an adapter molecule phosphorylated by various tyrosine kinases; Ref. 27). It remains to be determined whether protein-protein interactions modulate the sensitivity of Fak to caspase cleavage.

It is curious that the predominant caspase-3 consensus cleavage site identified in chicken and human Fak is absent in rodent Fak. Species alignments for several identified caspase substrates have revealed that in all cases examined, the P$_1$ aspartic acid in the caspase cleavage site was conserved. It remains to be determined whether the absence of this predominant caspase cleavage site in rodent Fak modulates the cellular responses to cell adhesion. Of interest is the report that the murine cell line, NIH3T3, is relatively resistant to anoikis (9).

Cleavage at either DQTD772 or VSVD704 generates carboxyl-terminal fragments that inhibit Fak phosphorylation and thus act like FRNK, the naturally occurring variant of Fak (Fig. 6D). Results presented in this report suggest two mechanisms by which Fak-mediated cellular responses to cell adhesion are abrogated during apoptosis: (i) by decreasing the overall amount of Fak in the cell and (ii) by generating fragments that act as competitive inhibitors of the remaining full-length Fak protein. That the cell has devised two mechanisms to inactivate Fak underscores the importance of this cleavage event in the execution of apoptotic cell death. We propose that the disabling of Fak liberates the cell from anti-apoptotic signals generated by the extracellular matrix and allows removal of the apoptotic cell from the tissue.

Acknowledgments—We thank Dr. Michael D. Schaller for helpful comments during the course of this work. We thank Isolde Seiden and Vicky Houtzager for sequencing some of the constructs used in this study.

REFERENCES

1. Otey, C. A. (1996) Int. Rev. Cytol. 167, 161–183
2. Cobb, B. S., Schaller, M. D., Leu, T.-H., and Parsons, J. T. (1994) Mol. Cell. Biol. 14, 147–155
3. Xing, Z., Chen, H.-C., Nowlen, J. K., Taylor, S. J., Shalloway, D., and Guan, J.-L. (1994) Mol. Cell. Biol. 5, 413–421
4. Chen, H.-C., and Guan, J.-L. (1994) Proc. Natl. Acad. Sci. U. S. A. 91, 10148–10152
5. Guinebault, C., Pavastre, B., Racaud-Sultan, C., Mazarguil, H., Breton, M., Mauro, G., Plantavid, M., and Chap, H. (1995) J. Cell Biol. 129, 831–842
6. Schlaepfer, D. D., Hanks, S. K., Hunter, T., and Van der Geer, P. (1994) Nature 372, 768–791
7. Schaller, M., Bergman, C. A., and Parsons, J. T. (1993) Mol. Cell. Biol. 13, 786–799
8. Richardson, A., and Parsons, J. T. (1996) Nature 380, 538–540
9. Frisch, S. M., Vuori, K., Runslahl, E., and Chan-Hui, P.-Y. (1996) J. Cell. Biol. 134, 793–799
10. Hungerford, J. E., Compton, M. T., Matter, M. L., Hoffstrom, B. G., and Otey, C. A. (1996) J. Cell Biol. 135, 1283–1290
11. Owens, L. V., Xu, L., Craven, R. J., Dent, G. A., Weiner, T. M., Kornberg, L., Liu, E. T., and Cance, W. G. (1995) Cancer Res. 55, 2752–2755
12. Owens, L. V., Xu, L., Dent, G. A., Yang, X., Sturge, G. C., Craven, R. J., and Cance, W. G. (1996) Ann. Surg. Oncol. 3, 100–105
13. Weiner, T. M., Liu, E. T., Craven, R. J., and Cance, W. G. (1993) Lancet 342, 1024–1025
14. Weiner, T. M., Liu, E. T., Craven, R. J., and Cance, W. G. (1994) Ann. Surg. Oncol. 1, 18–27
15. Xu, L.-H., Owens, L. V., Sturge, G. C., Yang, X., Liu, E. T., Craven, R. J., and Cance, W. G. (1996) Cell Growth Diff. 7, 413–418
16. Crouch, D. H., Fincham, V. J., and Frame, M. C. (1994) Oncogene 12, 2689–2696
17. Ohnishi, D., and Thornberry, N. A. (1997) Trends Biochem. Sci. 22, 299–306
18. Ho, S. N., Hunt, H. D., Horton, R. M., Pullen, J. K., and Pease, L. R. (1989) Gene (Amst.) 77, 51–59
19. Groger, R., Morrow, D. M., and Tykoczinski, M. L. (1989) Gene 81, 285–294
20. Thornberry, N. A., Rano, T. A., Peterson, E. P., Rasper, D. M., Timkey, G., Garcia-Calvo, M., Houtzager, V. M., Nordstrom, P. A., Roy, S., Vaillant-Cousin, J. P., Chapman, K. T., and Nichelson, D. W. (1997) J. Biol. Chem. 272, 17907–17911
21. Lazebnik, Y. A., Kaufmann, S. H., Desnoyers, S., Porier, G. G., and Earnshaw, W. C. (1994) Nature 371, 346–347
22. Nicholson, D. W., Ali, A., Thornberry, N. A., Vaillant-Cousin, J. P., Ding, C. K., Gallant, M., Gareau, Y., Griffin, P. R., Labelle, M., Lazebnik, Y. A., Munday, N. A., Raju, S. M., Smulski, E. M., Vamin, T.-T., Yu, V. L., and Miller, D. K. (1995) Nature 376, 37–43
23. Richardson, A., Malik, R. K., Hildebrand, J. D., and Parsons, J. T. (1997) Mol. Cell. Biol. 17, 6906–6914
24. Hildebrand, J. D., Taylor, J. M., and Parsons, J. T. (1996) Mol. Cell. Biol. 16, 3169–3178
25. Hartle, M. T., Hildebrand, J. D., Burnham, M. R., Bouton, A. H., and Parsons, J. T. (1996) J. Biol. Chem. 271, 13649–13655
Caspases Cleave Focal Adhesion Kinase during Apoptosis to Generate a FRNK-like Polypeptide
François G. Gervais, Nancy A. Thornberry, Salvatore C. Ruffolo, Donald W. Nicholson and Sophie Roy

J. Biol. Chem. 1998, 273:17102-17108.
doi: 10.1074/jbc.273.27.17102

Access the most updated version of this article at http://www.jbc.org/content/273/27/17102

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 27 references, 13 of which can be accessed free at http://www.jbc.org/content/273/27/17102.full.html#ref-list-1