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AT motif binding factor 1 (ATBF1) is highly phosphorylated in embryonic brain and protected from cleavage by calpain-1

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ABSTRACT

ATBF1 is a transcription factor that regulates genes responsible for repairing tissues and the protection of cells from oxidative stress. Therefore reduction of ATBF1 promotes susceptibility to varieties of human diseases including neurodegenerative diseases and malignant tumors. The instability of the protein was found to be an important background of diseases. Because ATBF1 is composed of a large 404-kDa protein, it can be easily targeted by proteinases. The protein instability should be a serious problem for the function in the cells and practically for our biochemical study of ATBF1. We have found that calpain-1 is a protease responsible for the degeneration of ATBF1. We observed distinct difference between embryo and adult brain derived ATBF1 regarding the sensitivity to calpain-1. The comparative study showed that eight phosphorylated serine residues (Ser1600, Ser2634, Ser2795, Ser2804, Ser2900, Ser3431, Ser3613, Ser3697) in embryonic brain, but only one site (Ser2634) in adult brain. As long as these amino acids were phosphorylated, ATBF1 derived from embryonic mouse brain showed resistance to cleavage; however, treatment with calf intestine alkaline phosphatase sensitized ATBF1 to be digested by calpain-1. An inhibitor (FK506) against calcineurin, which is a serine/threonine specific phosphatase enhanced the resistance of ATBF1 against the digestion by calpain-1. Taken together, these results demonstrate that these phosphorylation sites on ATBF1 function as a defensive shield to calpain-1.

1. Introduction

AT motif binding factor 1 (ATBF1, also called ZFHX3) is a 404-kDa transcription factor that contains four homeodomains and 23 zinc finger motifs [1]. A small alternatively-spliced product from the *ATBF1* gene was first identified as one of the DNA binding factors interacting with an AT-rich element located upstream of alpha-fetoprotein (*AFP*) promoter to suppress gene transcription [2]. Because of its ability to suppress *AFP* gene transcription in hepatic cells, ATBF1 is a factor associated with differentiation of the hepatocyte. We observed expression of ATBF1 in the brains of developing embryos, but its expression is dramatically reduced in adult brain [3,4]. Therefore we suggested that ATBF1 is specifically important for embryonic brain, but that it might not play an essential role in adult brains [4].

ATBF1 is expressed in a variety of adult organs, and abnormalities of ATBF1 have been linked to many human chronic diseases. ATBF1 may have another role in adult organs to maintain a healthy body. In fact, ATBF1 plays an essential role as an oncosuppressor in adult tissues. The *ATBF1* gene, which has been assigned to chromosome 16q22.3-23.1, was identified as a plausible candidate tumor suppressor for prostatic cancer [5]. Accordingly, abnormalities of ATBF1 are associated with various cancers, including gastric cancer [6–8], hepatocellular carcinoma [9], breast cancer [10–12], and neuroblastoma [13]. Besides cancers, abnormalities of ATBF1 induce susceptibility to Kawasaki disease [14], atrial fibrillation and ischemic stroke [15,16], schizophrenia [17], and ataxia telangiectasia [18]. Because ATBF1 regulates more than 200 genes responsible for repairing tissues and organizing protective responses to

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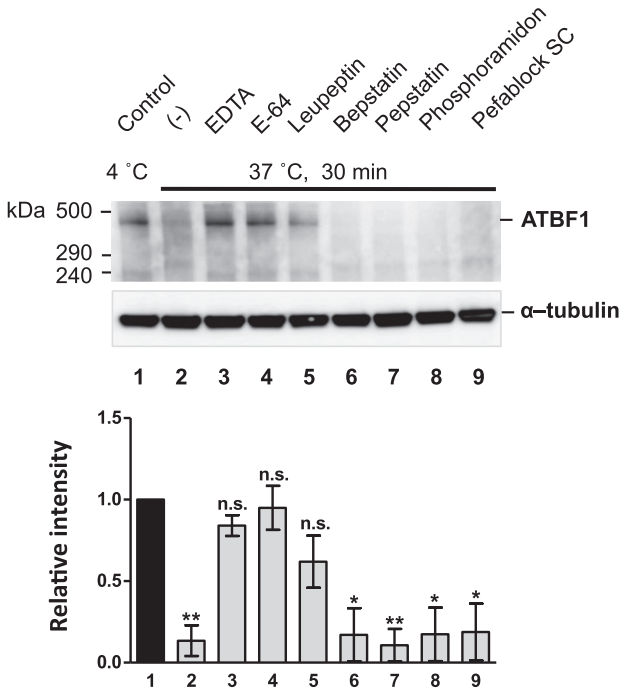

Fig. 1. Serine protease inhibitors block the degradation of ATBF1. Total amounts of 20 μg of adult mouse brain lysates were treated with EDTA (lane 3), E-64 (lane 4), leupeptin (lane 5), bestatin (lane 6), pepstatin (lane 7), phosphoramidon (lane 8), or Pefabloc SC (lane 9) at 37 °C for 30 min and without any protease inhibitor (lane 2). Internal controls were detected by an anti-α-tubulin antibody using original lysates kept at 4 °C without adding any protease inhibitors to show original amount of proteins. The bar graph below corresponds to intensities of the bands with means and standard deviations from three independent experiments. n.s., Not significant; $^{*}p < 0.05$; $^{**}p < 0.01$.

oxidative stress, it should be involved in a variety of human chronic diseases [18].

This report presents results on studies of the stability of ATBF1 regulated by phosphorylations.

2. Materials and methods

2.1. Animals

Fourteen-day's pregnant ICR mice were used to extract the adult mouse brain proteins and embryonic mouse brain proteins from the mother and its babies, respectively. All experiments were performed in accordance with the Guidelines for Animal Experiments of the Animal Experimentation Committee of the National Center for Geriatrics and Gerontology. Mouse brains were rapidly taken out from the skull on ice. Mouse brain tissues were washed with ice-cold PBS washing buffer [137 mM NaCl, 2.7 mM KCl, 4.3 mM Na_2PHO_4, 1.4 mM KH_2PO_4]. After washing, tissue samples were homogenized using a mini-cordless grinder (Funakoshi, Tokyo, Japan) in ice-cold TNE buffer [20 mM Tris–HCl (pH 7.4), 150 mM NaCl, 2 mM EDTA, 1% nonident-P40 (Sigma, Saintlouis, Missouri, United States), 50 mM NaF] with 20 μM chymostatin (Calbiochem, Darmstadt, Germany). Homogenates were incubated on ice for 30 min, and then centrifuged at 15,000 × *rpm* for 30 min at 4 °C. The supernatants were used for further analysis.

2.2. Cell culture and transfection

The human embryonic kidney cell line HEK293T cells were grown in D-MEM supplemented with 10% fetal bovine serum (Invitrogen, Carlsbad, California, United States) at 37 °C and 5% CO_2. HEK293T cells were transfected with HA-tagged expression vector or HA-tagged ATBF1 expression vector (HA-ATBF1) [4] using transIT-293 reagent (Mirus, Madison, Wisconsin, United States) according to the manufacturer's instructions.

2.3. Western blotting analysis

We measured protein concentration using a Bradford assay kit (Bio-Rad, Hercules, California, United States). For protein detection, each sample was separated on a 4–20% gradient SDS–polyacrylamide gel (Bio-Rad, Hercules, California, United States), and the proteins were transferred to a polyvinylidene difluoride membrane (Millipore, Billerica, Massachusetts, United States). The membrane was blocked with 5% bovine serum albumin (BSA) (Fraction V, Sigma, Saint louis, Missouri, United States) in Tris-buffered saline containing 0.05% Tween 20 for 1 h, and then incubated with primary antibodies for 1 h at room temperature. All antibodies were diluted in 1% BSA in Tris-buffered saline containing 0.05% Tween 20. Rabbit polyclonal anti-ATBF1 antibodies (D1-120 at 1:1000 and AT-6 at 1:2000) (Catalog No. PD010 and PD011, MBL, Nagoya, Japan) were used. Mouse monoclonal anti-α-tubulin antibody was used at a dilution of 1:8000 (Catalog No. M175-3, MBL, Nagoya, Japan). The membrane was incubated with secondary antibodies, namely, goat anti-mouse IgG (H + L-chain)-HRP antibody at 1:4000 (Catalog No. 330, MBL, Nagoya, Japan) or goat anti-rabbit IgG (H + L-chain)-HRP antibody at 1:2000 (Catalog No. 458, MBL, Nagoya, Japan), for 1 h at room temperature, and visualized sing Amersham ECL Plus (GE Healthcare, Buckinghamshire, United Kingdom) and a LAS-3000 image analyzer (Fuji Photo Film, Tokyo, Japan).

2.4. [^{32}P] orthophosphate labeling

About 1.0×10^7 transfected HEK293 cells were collected, washed with 5 ml of 10% serum phosphate-free D-MEM (Gibco, Grand Island, New York, United States) twice, and then incubated with 0.5 mCi [^{32}P] orthophosphate (GE Healthcare, Buckinghamshire, United Kingdom) at 37 °C for 2 h. Cells were washed twice in PBS, lysed by ice-cold TNE buffer containing Protease Inhibitor Cocktail (1 tablet used in 10 ml lysate) (Roche, Basel, Switzerland), and then centrifuged at 14,000 × *rpm* for 5 min at 4 °C to separate debris. Then, 1 mg of total protein per sample was incubated for 16 h at 4 °C with protein G-Sepharose beads (GE Healthcare, Buckinghamshire, United Kingdom) conjugated to 5 μg of anti-ATBF1 antibodies (AT-6) (MBL, Nagoya, Japan). The immunoprecipitation products were boiled in SDS sample buffer and separated on 4–20% gradient SDS–polyacrylamide gels. Half of the sample was transferred to a membrane and detected using anti-ATBF1 antibody (AT-6). The other half of the sample was separated on 4–20% gradient SDS–polyacrylamide gels and subjected to autoradiography.

2.5. Protease inhibitors

Adult mouse brain was lysed using ice-cold lysis buffer [20 mM Tris–HCl (pH 7.4), 150 mM NaCl, 1% nonident-P40 (Sigma), 50 mM NaF]. After lysis, 20 μg aliquots of mouse brain protein extracts were treated with protease inhibitors (Roche, Basel, Switzerland), including 5 μg/ml E-64, 10 μg/ml leupeptin, 10 μg/ml bestatin, 10 μg/ml pepstatin, 5 mg/ml phosphoramidon, 5 mg/ml Pefabloc SC and 0.6 mg/ml EDTA in a 10 μl reaction system, at 37 °C for 30 min, to screen for the major proteases responsible for the degradation of ATBF1. The reaction was stopped by addition of SDS–PAGE sample buffer and boiling at 99 °C for 5 min. Degraded products were analyzed by Western blot analysis using anti-ATBF1 antibody (D1-120) to determine the ATBF1 protein levels.

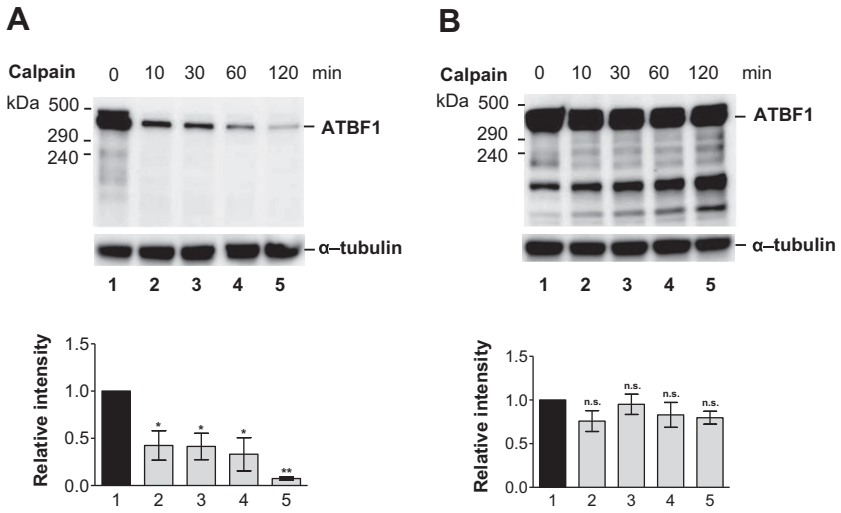

Fig. 2. Adult mouse brain-derived ATBF1 is sensitive, but embryonic mouse brain-derived ATBF1 is resistant to calpain-1. Total amounts of 20 μg of samples were treated with calpain-1 at 20 °C for each indicated period. (A) The adult mouse brain lysates were treated with calpain-1 for 0 min (lane A1), 10 min (lane A2), 30 min (lane A3), 60 min (lane A4), and 120 min (lane A5). (B) The Embryonic mouse brain lysates were treated with calpain-1 for 0 min (lane B1), 10 min (lane B2), 30 min (lane B3), 60 min (lane B4), and 120 min (lane B5). The reaction was stopped by addition of SDS–PAGE sample buffer and total level of ATBF1 was examined by Western-blots using anti-ATBF1 antibody (D1-120). Internal controls (panels A and B) were detected by an anti-α-tubulin antibody using lysates kept at 4 °C without treatment with calpain-1 to show original amount of proteins. The bar graph below corresponds to the intensities of the bands with means and standard deviations from three independent experiments. n.s., Not significant; $^{*}p < 0.05$; $^{**}p < 0.001$.

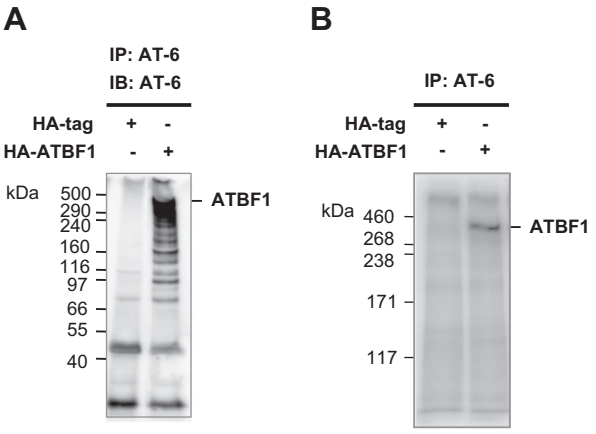

Fig. 3. Full-length 404-kDa ATBF1 is phosphorylated, but its fragments are not phosphorylated. (A) Full-length ATBF1 cDNA (12-kb) expression vector (HA-ATBF1) or HA-tag expression vector was transfected into HEK293T cells and the protein was immunoprecipitated by anti-ATBF1 antibody (AT-6), then detected using the same antibody (AT-6). (B) HEK293T cells were transfected with a full-length ATBF1 cDNA (12-kb) expression vector (HA-ATBF1) or HA-tag-containing vector and then labeled with [^{32}P]-orthophosphate at 37 °C for 2 h before immunoprecipitation with anti-ATBF1 antibody (AT-6) and autoradiography.

2.6. Calpain treatment

Aliquots of 60 μg of mouse brain lysates were incubated in 30 μl of calpain reaction buffer [63 mM imidazol–HCl, pH 7.3, 10 mM β-mercaptoethanol, 5 mM $CaCl_2$] with μ-calpain (Calpain-1, Cat. No. 208713, Calbiochem Darmstadt, Germany) at a final concentration of 0.256 μg/μl. After dividing the reaction mixture into a final volume of 10 μl per reaction, the samples were incubated at 20 °C for each experimental period.

2.7. Statistics

The results of Western blotting were normalized based on the expression levels of α-tubulin and are depicted as means ± s.e.m from at least three independent experiments. Statistical significance was assessed by the Student's *t*-test and is indicated as $^{*}p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.001$; n.s. not significant.

3. Results

3.1. Serine protease inhibitors block the degradation of ATBF1

To screen for the enzymes responsible for the degradation of ATBF1, a set of protease inhibitors, including bestatin, E-64, leupeptin, pepstatin, phosphoramidon, Pefabloc SC and EDTA were applied to lysates from adult mouse brain in vitro. Among the protease inhibitors, E-64, leupeptin, and EDTA specifically inhibited the degradation of ATBF1 (Fig. 1). E-64 irreversibly inhibits a wide range of cysteine peptidases including papain, cathepsin B, cathepsin L, staphopain and calpains [19]. Leupeptin inhibits cysteine, serine and threonine peptidases including plasmin, kallikrein, papain, and calpains. EDTA chelates metal ions and inhibits calcium-induced activity of calpains. Considering these criteria, calpains were candidate enzymes for the degradation of ATBF1. We then proceeded to investigate the response of ATBF1 to calpain-1 in vitro, because activation of calpain-1 converts excitotoxic neuronal death into caspase-independent cell death [20].

3.2. Embryonic mouse brain-derived ATBF1 is resistant to calpain-1

The hyperactivation of calpains is implicated in a number of pathologies associated with altered calcium homeostasis such as Alzheimer's disease [21]. The same amounts of proteins extracted from the brains of adult and embryo brains were then treated with the same amount of calpain-1 under the same conditions. Adult mouse brain-derived ATBF1 was sensitive to calpain-1 (Fig. 2A); on the contrary, embryonic mouse brain-derived ATBF1 was resistant to calpain-1 at any time period (Fig. 2B). It was our surprise to observe such a distinct difference of the sensitivity to calpain-1 between embryonic and adult brain derived ATBF1. This observation raised the issue for further consideration of what was the mechanism responsible for such a difference in sensitivity to calpain-1 between adult and embryo proteins.

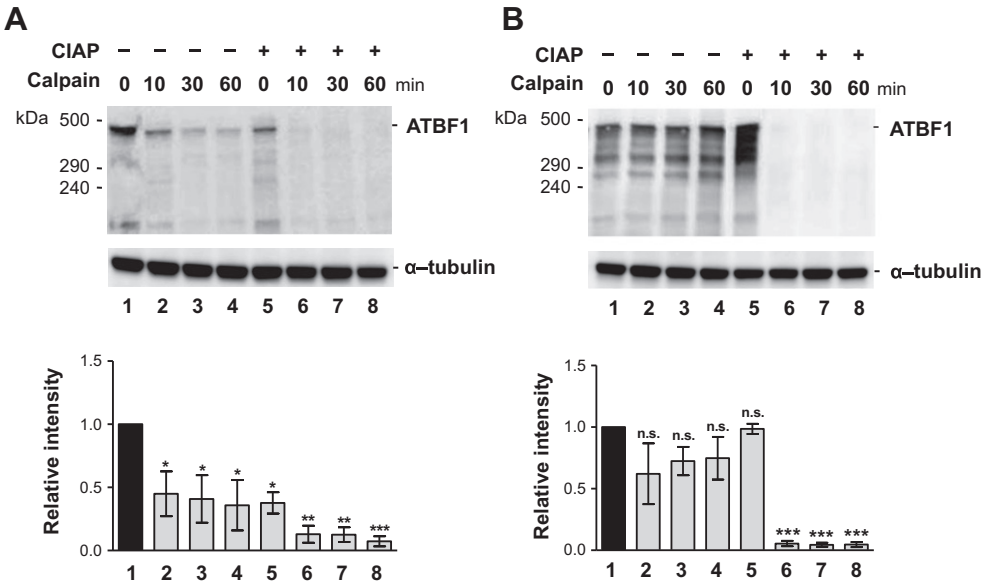

Fig. 4. Dephosphorylation increases the sensitivity to calpain-1. Total amounts of 20 μg of samples were treated with calpain-1at 20 °C for each indicated period. (A) Adult mouse brain lysates were treated with calpain-1 for 0 min (lane A1), 10 min (lane A2), 30 min (lane A3), and 60 min (lane A4). Samples were subjected to pre-incubation with calf intestinal alkaline phosphatase (CIAP; 1 unit/μl) at 37 °C for 30 min, and then treated with calpain-1 for 0 min (lane A5), 10 min (lane A6), 30 min (lane A7), and 60 min (lane A8). (B) Total amounts of 20 μg of embryonic mouse brain lysates were treated with calpain-1 for 0 min (lane B1), 10 min (lane B2), 30 min (lane B3), and 60 min (lane B4). Samples were subjected to pre-incubation with calf intestinal alkaline phosphatase (CIAP; 1 unit/μl) at 37 °C for 30 min, and then treated with calpain-1 for 0 min (lane B5), 10 min (lane B6), 30 min (lane B7), and 60 min (lane B8). The reaction was stopped by addition of SDS/PAGE sample buffer and total levels of ATBF1 were examined by Western-blots using anti-ATBF1 antibody (D1-120). Internal controls (panels A and B) were detected by an anti-α-tubulin antibody using lysates kept at 4 °C without treatment with calpain-1 to show original amount of proteins. The bar graph below corresponds to the intensities of the bands with means and standard deviations from three independent experiments. n.s. Not significant; $^{*}p < 0.05$; $^{**}p < 0.005$; $^{***}p < 0.001$.

3.3. ATBF1 is hyperphosphorylated in embryonic mouse brain

Calpastatin suppresses the activity of calpain-1 in vivo. The expression level of calpastatin in adult mouse is significantly higher than that in embryonic mouse brain [22]. However, the higher sensitivity of adult brain-derived ATBF1 cannot be explained by contamination with calpastatin in the experimental system. We assumed that protein modifications of ATBF1 would provide a clue to understanding the mechanism underlying the resistance of embryonic ATBF1 to calpain-1. We prepared full-size ATBF1 by transfection of HEK293T cells with ATBF1 cDNA. We successfully detected full-size ATBF1 as an immunoprecipitated product at a molecular weight of 404 kDa and, unexpectedly, we also detected many small fragments (Fig. 3A). The same immunoprecipitated product showed that only full-length ATBF1 was labeled by [^{32}P]-orthophosphate (Fig. 3B). In contrast, the smaller fragments were not phosphorylated. These data suggest that the phosphorylation of ATBF1 is a key mechanism for the protection of ATBF1 from degradation.

3.4. Dephosphorylation increases the sensitivity of ATBF1 to calpain-1

If the hyperphosphorylated status is the major protective mechanism against digestion by calpain-1, treatment with phosphatase will restore the sensitivity of ATBF1 to calpain-1. Brain lysates were pre-treated with calf intestinal alkaline phosphatase (CIAP) before treatment with calpain-1. The sensitivity to calpain-1 was enhanced for both adult brain-derived ATBF1 (Fig. 4A) and embryonic brain-derived ATBF1 (Fig. 4B). We concluded that the level of phosphorylation of ATBF1 affected its sensitivity to calpain-1, explaining the difference between embryo and adult proteins. To confirm the hyperphosphorylation of ATBF1 in embryos, we examined protein modifications by mass spectrometry. We identified eight phosphorylated serine residues (Ser1600, Ser2634, Ser2795, Ser2804, Ser2900, Ser3431, Ser3613, Ser3697) in ATBF1 derived from embryonic brain, and only one site (S2634) in ATBF1 derived from adult brain (Table S1).

4. Discussion

This result suggested that the cleavage of ATBF1 was strongly associated with the elevation of calcium ions. Although calpains were good candidates for the digestion of ATBF1, we could not determine whether ATBF1 was really a target of calpain-1 simply by searching its amino acid sequence. There is no specific amino acid sequence uniquely recognized by calpain-1. Amongst protein substrates, tertiary structure elements rather than amino acid sequence are likely to be responsible for directing cleavage to a specific substrate [23]. Therefore, we cannot tell whether ATBF1 is a target of calpain-1 unless we perform direct experiments in vitro. First, we obtained reasonable results by using ATBF1 derived from adult to show the digestion of ATBF1 by calpain-1. However, when we investigated further the fine process of digestion by calpain-1 using ATBF1 derived from embryonic brain, we realized that embryonic and adult mouse-derived ATBF1 show different sensitivities to calpain-1. Pioneering work on the phosphorylation of p35 as a switching mechanism to alter the sensitivity to calpain-1 to distinguish embryonic and adult brain [24] was a great hint to consider the phosphorylation status of ATBF1.

Although the first evidence of phosphorylation of ATBF1 was at Ser1180 associated with DNA double strand breaks as a target of ATM, eight newly identified independent serine/threonine phosphorylation sites (Table S1) had no consensus sequences as targets of ATM, but other kinase(s) should work for the modification. The responsible kinase(s) is the next issue remaining to be solved. An inhibitor against the serine/threonine phosphatase (FK506) will be a good candidate for stabilizing ATBF1. FK506 has been reported to suppress the pathological progression of Alzheimer disease [25]. We assumed that the treatment with FK506 should increase the stability of ATBF1 and contribute to cure the ATBF1 related

diseases. We have observed an inhibitory effect of FK506 against degradation of ATBF1 by calpain-1 in a dose-dependent manner (Fig. S1).

We initially thought that both calpains and caspases might be responsible for the cleavage of ATBF1, because both classes of enzymes are cysteine proteases blocked by E64 and leupeptin, and they share many similar substrates. Caspases are essential for caspase-dependent apoptotic death whereas calpains may play an augmentative role [22]. The primary candidate was caspase-3, because we found ten sites (initial aspartic acid at Asp-589, 956, 1498, 2024, 2259, 2367, 2763, 28313, 2939) fitting the consensus target sequence (Asp-X-X-Asp) [26] for caspase-3 in the amino-acid sequence of ATBF1. Unexpectedly, ATBF1 was not cleaved under the conditions of caspase-3 activation induced by A23187 (a calcium ionophore) [27]. Instead, we observed strong degradation of ATBF1 in the presence of a high concentration of A23187 without activation of caspase-3 (Fig. S2).

In this paper, we provided evidence that phosphorylation of ATBF1 was an important regulatory mechanism protecting it from digestion by calpain-1, distinguishing embryo and adult animals (Fig. S3). We hope these basic studies will provide a further understanding of varieties of human diseases with abnormalities of ATBF1.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2012.09.092.

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