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ORIGINAL ARTICLE

Selection and Application of DNA Aptamer Against Oncogene Amplified in Breast Cancer 1

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Abstract Amplified in breast cancer 1 (AIB1), also known as steroid receptor coactivator 3 (SRC-3), is a transcriptional coactivator that interacts with nuclear receptors and other transcription factors to enhance their effects on target gene transcription. AIB1, which acts as a major oncogene, is highly expressed in many human cancers, and has been demonstrated to be a key regulator for tumor initiation, progression, metastasis, invasion, and survival. Recruitment of the transcriptional factor CBP/p300 by CBP/p300-interaction domain (CID) of AIB1 is essential for its transcriptional activation function. In this research, we isolated a DNA aptamer AY-3 that binds to AIB1-CID from a random oligonucleotide library using in vitro screening technology—Systematic Evolution of Ligands by EXponential enrichment (SELEX). The binding affinity of the aptamer to AIB1-CID fusion protein is in the nanomolar range. More importantly, the aptamer was found to disrupt in the interaction between p300 and AIB1. This aptamer has great potential to serve as a therapeutic agent for cancer by inhibiting the coactivation of AIB1.

Keywords AIB1 · Aptamer · SELEX · Cancer

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Introduction

Amplified in breast cancer 1 (AIB1/SRC-3/N-coR/ACTR) (Guan et al. 1994; Planas-Silva et al. 2001; Suen et al. 1998), as a member of the p160 coactivator family that also includes SRC-1 (NcoA-1) (Litterst and Pfitzner 2001) and SRC-2 (GRIP1/TIF2) (Voegel et al. 1998), is a cancer-amplified coactivator. AIB1 interacts with nuclear receptors and certain other transcription factors, recruits histone acetyltransferases and methyltransferases for chromatin remodeling, and facilitates target gene transcription. It is correlated with increased cancer cell proliferation, survival, migration, and invasiveness, all of which play important roles in the progression of many cancers such as prostate cancer (Zhou et al. 2005), breast cancer (Anzick et al. 1997), colorectal cancer (Mo et al. 2015; Xie et al. 2005), and hepatocellular carcinoma (Xu et al. 2010).

AIB1 can interact with nuclear receptors and other transcription factors to regulate the expression of their target genes involved in many signaling pathways, including ERα, EGFR, Akt, MAPK, E2F1, C/EBPβ, NF-κB, HER2/neu, PEA3, and CBP/p300 (Chen et al. 1997; Kishimoto et al. 2005; Long et al. 2012; Long et al. 2010; Louie et al. 2004; Wu et al. 2002; Yan et al. 2006a, b). AIB1 is also a master regulator of human cancer growth. It has been reported that AIB1 is overexpressed in 35 and 68 % of colorectal cancer tissues and hepatocellular

carcinoma tissues, respectively, and promotes cancer progression by enhancing cell proliferation and invasiveness (Xu et al. 2010). Downregulation of AIB1 suppresses cancer cell proliferation, inhibits cancer cell cycle progression, and reduces cancer cell migration and invasion (Xu et al. 2010). On the other hand, upregulation of AIB1 enhances the expression of proliferating cell nuclear antigen (PCNA) and matrix metalloprotein 9 (MMP-9) (Xu et al. 2010).

The C-terminus of the p160 coactivator family contains two transcriptional activation domains (AD). AD1, also known as CBP (cAMP-response element binding protein)/p300 interaction domain (CID), is the essential domain for recruiting coactivator with histone acetyltransferase activity like CBP/p300 and p/CAF (p300/CBP associated factor) (Liao et al. 2002). AD2 activity is apparently mediated through coactivator-associated arginine methyltransferase 1 (CARM1). It was reported that sequential recruitment of p160 coactivator family and CBP/p300 to the ligand-bound nuclear receptor leads to enhanced chromatin remodeling and elevated transcription (Liu et al. 1999, 2001). CBP/p300 may activate the transcription machinery through its histone acetyltransferase (HAT) activity which acetylates histones and other proteins involved in transcription (Li et al. 2000). The full length of AIB1 can strongly augment glucocorticoid receptor induction of the mouse mammary tumor virus (MMTV) reporter, but the CID deletion mutant shows no effect above background because of the unbound CBP/p300 on AIB1-CID (Chen et al. 1997). Mutation of LXXLL (α-helix motif in CID) motif is significantly reduced CID transcriptional activity (Voegel et al. 1998). Thus, the recruitment of CBP/p300 on the nuclear receptor is essential for transactivation of AIB1. Inhibition of its transactivation function by reducing the recruitment of CBP/p300 may be a strategy for cancer prognosis and treatment (Tien and Xu 2012).

Recently, aptamers, a new class of molecular probes, have attracted the attention of researchers and clinicians. Aptamers are single-stranded oligonucleotides isolated by an in vitro screening technology called Systematic Evolution of Ligands by EXponential enrichment (SELEX) (Tuerk and Gold 1990). SELEX involves the progressive selection of aptamers by repeated rounds of partitioning and amplification from a random single-strand oligonucleotide library. Based on the tertiary structures formed by the single-stranded oligonucleotides, aptamers can selectively recognize a wide variety of molecules ranging from small organic molecules to proteins (Nutiu and Li 2005; Osborne and Ellington 1997; Wilson and Szostak 1999). Aptamers have many attractive features including high affinity and specificity, rapid and reproducible synthesis, flexible modification, biocompatibility, low toxicity, low immunogenesis, and in vitro stability (Jayasena 1999; Shangguan et al. 2007; Yan et al. 2005). Because of these advantages, aptamers show great potential for use in medical and pharmaceutical basic research, drug development, diagnosis, and therapy application (Fang and Tan 2010; Jayasena 1999; Rosenberg et al. 2014; Soundararajan et al. 2008; Wu et al. 2010; Yan et al. 2005).

Herein, we have successfully generated an aptamer against AIB1 CBP/p300-interaction Domain with equilibrium dissociation constants (K_d) in the nanomolar range. The selected aptamer AY-3 can bind to p160 coactivator family members which have functional domains similar to those of AIB1. Furthermore, Co-immunoprecipitation data demonstrated that the function of AIB1 recruiting p300 was suppressed by aptamer AY-3, suggesting that AY-3 is a potential molecule for treating AIB1-overexpressed cancer.

Materials and Methods

Cell Lines, Plasmids, and Buffers

The human embryonic kidney cell 293T was cultured in Dulbecco's Modified Eagle's Medium (DMEM, Hyclone) supplemented with 10 % fetal bovine serum (FBS, Hyclone) and 100 U/mL penicillin–streptomycin at 37 °C in a humidified atmosphere containing 5 % CO_2. The plasmids used in this project are pCR3.1-flag, pCR3.1-flag-AIB1, pCR3.1-flag-SRC-1, pCR3.1-flag-SRC-2, pCR3.1-flag, pCR3.1-flag-bHLH/PAS, pCR3.1-flag-S/T, pCR3.1-flag-RID, pCR3.1-flag-CID, and pCR3.1-flag-HAT.

Transfection and Protein Preparation

The 293T cells were transfected with plasmids listed in the previous paragraph by lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. After transfecting, cells were cultured according to the above processes for 24 h, and lysed with lysis buffer (Tris–HCl 20 mmol/L pH 7.5, NaCl 150 mM, EDTA 1 mM, EGTA 1 mM, TritonX-100 1 %, Sodium pyrophosphate 2.5 mM, β-glycerophosphate 1 mM, $NaVO_4$ 1 mM, Leupeptin 1 μg/mL, PMSF 1 mM). Total cell lysate of the control group and target flag-AIB1-CID group was incubated with flag M2 beads (ANTI-FLAG® M2 Affinity Gel Sigma-Aldrich, A2220) for 3 h at 4 °C followed by three washes. The flag M2 beads coupled with flag-tagged protein were kept at 4 °C in a moist environment until use. The flag-tagged protein couple status was tested by Western Blotting.

SELEX Procedures

The HPLC-purified DNA library synthesized by Sangon Biotech (Shanghai) contained a central randomized sequence of 40 nucleotides (nt) flanked by 20-nt primer hybridization sites (5′-AGC GTC GAA TAC CAC TAC AG-40N-CTA ATG GAG CTC GTG GTC AG-3′) (Hu et al. 2011). A fluorescein isothiocyanate (FAM)-labeled 5′-primer (5′-FAM-AGC GTC GAA TAC CAC TAC AG-3′) and a biotinylated (Bio)-labeled 3′-primer (5′-Biotin-CTG ACC ACG AGC TCC ATT AG-3′) were used in the PCR reactions for the synthesis of labeled double-stranded DNA sequences. For the first selection round, 5 nmol initial ssDNA library was mixed thoroughly with 500 μL binding buffer (5 mM $MgCl_2$, 0.1 mg/mL yeast tRNA in PBS, pH 7.4), and the mixture was heated at 95 °C for 5 min and immediately cooled on ice for 10 min. First, the ssDNA pool was incubated with control beads for counter selection. Unbound ssDNA pool was collected by filtering with a home-made column. Flag M2 beads coupled to flag-AIB1-CID (1×10^5) were incubated with the unbound ssDNA pool at 37 °C on a rotating vortex mixer. Beads were washed with washing buffer after incubation. The recovery of the sequences binding to flag-AIB1-CID beads was achieved by heating at 95 °C for 5 min in PCR water and then amplifying by PCR. The thermal cycling conditions were as follows: 94 °C for 3 min (initial denaturation), 10 cycles of 94 °C for 0.5 min, 53 °C for 0.5 min, and 72 °C for 0.5 min, followed by a single final extension at 72 °C for 5 min. In order to acquire aptamers with high affinity and specificity, the washing strength was enhanced gradually by increasing the volume of wash buffer and the number of washes. Additionally, the ssDNA amount of the library per round (200–150 pmol) was decreased. The potential aptamers bound to flag-AIB1-CID beads were then amplified by PCR with FAM-labeled forward primers and biotin-labeled reverse primers. After denaturing in 0.1 M NaOH, the selected ssDNA was separated from the biotinylated antisense ssDNA strand by streptavidin Sepharose beads (GE healthcare) and used for next round selection. The progress of the selection process was monitored using confocal imaging.

Confocal Imaging of Beads Stained with Aptamer

To characterize the specificity of the generated aptamers, fluorescence images of flag-tagged proteins bound with aptamers or unselected initial library labeled with FAM were captured using laser confocal fluorescence microscopy (Leica, Germany). Beads were exposed to 200 nM of FAM-labeled aptamers or unselected initial library in binding buffer 37 °C for 40 min in the dark. Supernatant was then removed and beads were washed twice with ice-cold washing buffer. Mean fluorescence intensity of beads was quantified by Image J software. The K_d of the fluorescent ligands were obtained by fitting the dependence of fluorescence intensity of specific binding on the concentration of the ligands to the equation $Y = B_{max}X/(K_d + X)$ (X is the DNA concentration/nM, Y is the mean fluorescence intensity) using the SigmaPlot 12.0 software.

Cloning and DNA Sequencing

After 12 rounds of selection, the fluorescence intensity of the enriched pool was noticeably greater than that of the initial pool. The enriched 12th ssDNA pool was PCR-amplified using unmodified primers for genome sequencing by Shanghai Sangon Biotech Co., Ltd. China. Using Clustal X 2.0.3 software, the resulted eighty sequences were subjected to multiple sequence alignment analysis to discover highly conserved motifs in groups of selected DNA sequences. The discovered consensus sequences with high repeats among the enriched pool were then chemically synthesized in house on a DNA synthesizer (POLYGEN, Langen, Germany) for further characterization.

Co-immunoprecipitation (Co-IP) Assay and Western Blotting Analysis

For Co-IP assay, cells were lysed with lysis buffer. The cell lysates were immunoprecipitated by flag M2 beads. The selected aptamer and random sequence were also added in the cell lysates to reach a final concentration of 2 μM. The mixture was incubated at 4 °C for 3 h. After extensive washing, the precipitates were analyzed by Western blotting. For Western blot analysis, equal amounts of protein lysates were subjected to SDS–PAGE and transferred onto nitrocellulose membranes. Blots were probed with the specific primary antibodies against flag (Sigma), HA (Sigma). After extensive washing, blots were then incubated with horseradish peroxidase-conjugated secondary antibody (Pierce) and visualized by chemiluminescence.

Results

Selection of DNA Aptamer Against AIB1

AIB1-CID gene sequence tagged with flag was joined into the mammalian expression vector pCR3.1. For the expression of flag-AIB1-CID fusion protein, 293T cells were transfected with pCR3.1-flag-AIB1-CID. Flag-AIB1-CID in transfected cell lysate was purified by flag M2 beads and detected by Western blotting (Fig. S1).

To obtain aptamers against AIB1-CID, flag-AIB1-CID fusion protein was precipitated by Sepharose beads with

flag antibody. The resulting flag-AIB1-CID beads were used as the positive target in SELEX, while the control group beads (prepared by incubation with the lysate of cells transfected with control vector plasmid, pCR3.1) were used as negative control to remove non-specific surface binding sequences. The process of in vitro Sepharose-bead-based SELEX is schematically illustrated in Fig. 1. In our selection, a library of single-stranded DNA that contained a 40-mer random sequence region flanked by two 20-mer PCR primer sequences was used to incubate with control beads for counter selection. The DNA bound with control beads was removed. Unbound DNA was collected to incubate with the target protein. After washing to remove unbound DNA, the bound DNA was amplified by PCR for the next round of selection. The progress of the selection process was monitored using a fluorescence confocal microscope. With increased numbers of selection cycles, increase in fluorescence intensity on the target beads was observed, while there was no observable binding of the control beads (Fig. 2a). The binding affinity of the enriched library after 12 rounds was determined to be in the nanomolar range ($K_d = 122.6 \pm 12.6$ nM, Fig. 2b, c). The enriched DNA pool was then cloned and sequenced.

Identification of Selected Aptamers for AIB1

In order to identify individual aptamer candidates, eighty clones were sequenced in our experiment. The alignment results showed that the sequences were found to distribute into eight families based on their homology, and many repeats were observed in each family. Eight sequences from different sequence families were chosen for further characterization. Most of these sequences bind with flag-AIB1-CID beads, but not with control beads (Table S1). Based on their base sequences and structural characteristics, we chose AY-3, 5′-AGCGTCGAATACCACTACAG GGGATGCGAAGTTCCGCGGTCGAGTATATGATAC ATCCATCTAATGGAGCTCGTGGTCAG-3′ for further characterization. As shown in Fig. 3, AY-3 can recognize AIB1 with high affinity ($K_d = 47.83 \pm 4.99$ nM), while displaying negligible binding affinity for control beads.

Selected Aptamer Can Recognize p160 Family Proteins Specifically

To test binding specificity of our AIB1-CID aptamer AY-3, we studied the interaction of AY-3 with AIB1 functional

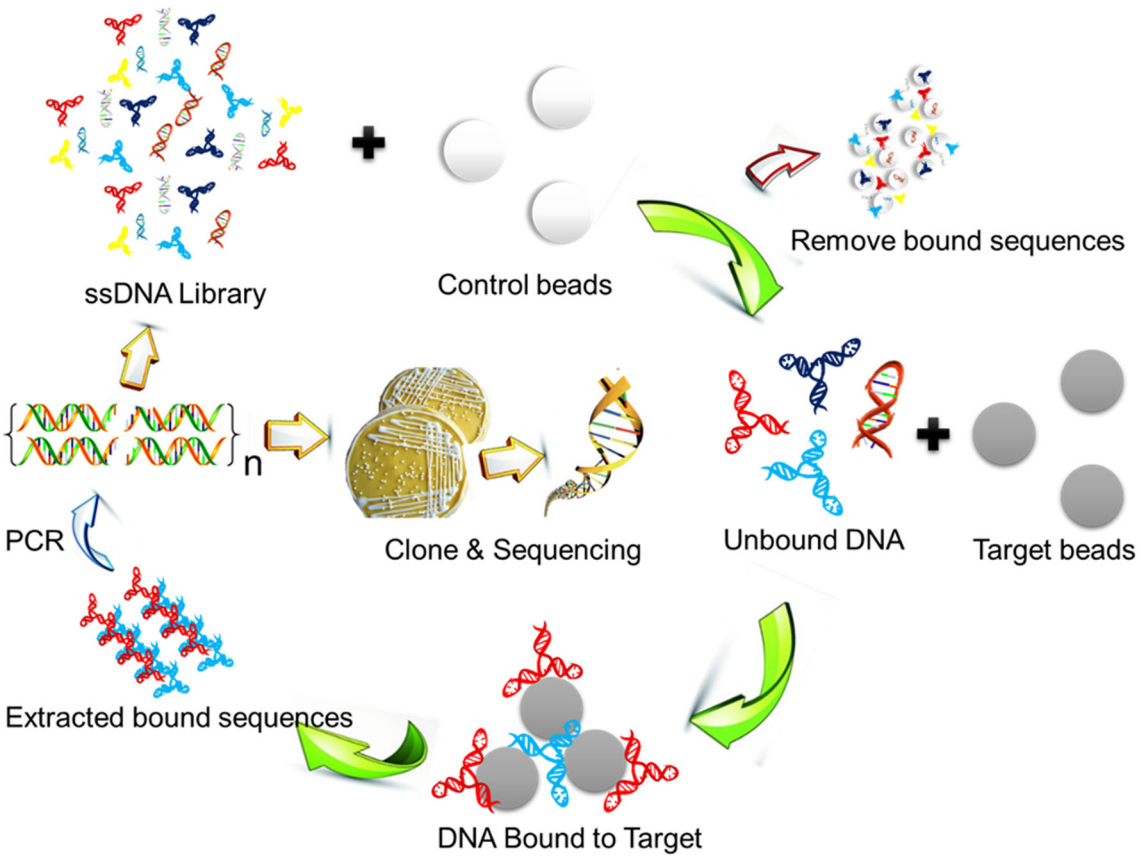

Fig. 1 Sepharose-bead-based SELEX process for protein AIB1

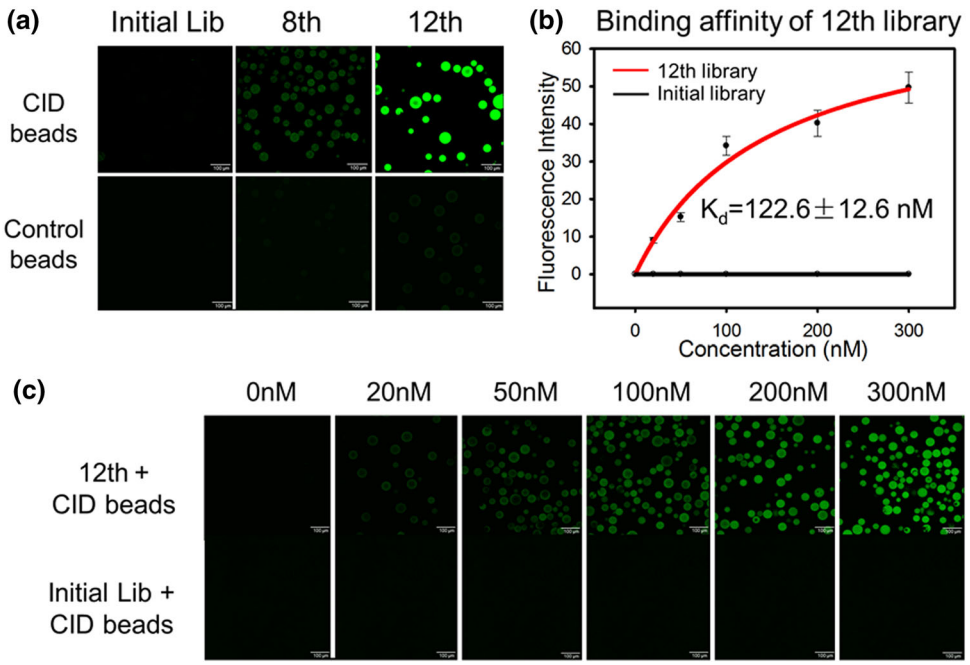

Fig. 2 The progress of the selection process monitored by confocal imaging. **a** The results of flag-AIB1-CID beads and control beads reacted with initial library, 8th, and 12th pool (200 nM), respectively. **b** Determination of the dissociation constant of the enriched pool to flag-AIB1-CID beads. *Red curve* 12th round enriched pool, *Black curve* Initial library. **c** Confocal images of flag-AIB1-CID beads with various concentrations of initial library and 12th pool (Color figure online)

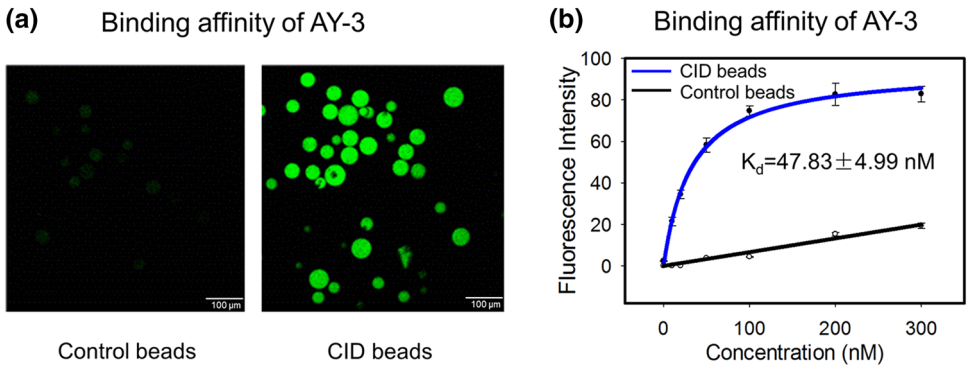

Fig. 3 Binding affinity of selected aptamer AY-3 to flag-AIB1-CID. **a** Confocal imaging result of flag-AIB1-CID beads and control beads reacted with AY-3 (200 nM). **b** Dissociation constant of AY-3. *Blue curve* Enriched aptamer AY-3, *Black curve* Control beads (Color figure online)

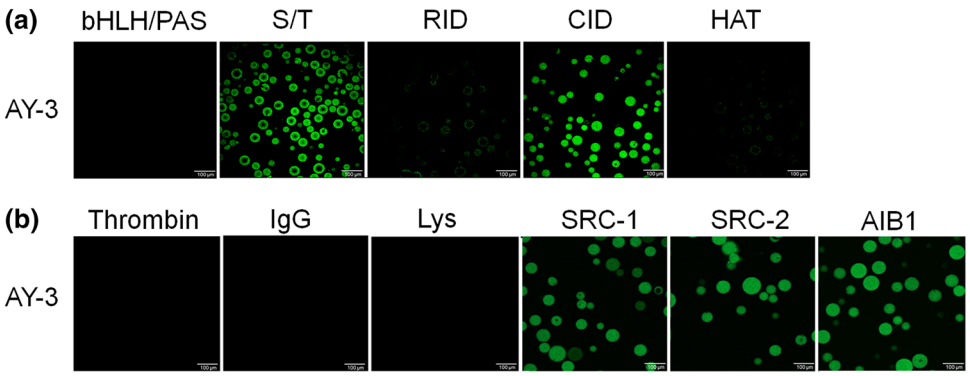

Fig. 4 Confocal imaging for investigating the specificity of aptamer AY-3. **a** AY-3 binding to five functional domains of AIB1, bHLH/PAS, S/T, RID, CID, and HAT. **b** AY-3 binding to p160 family members (AIB1, SRC-1, SRC-2), thrombin, immune globulin G (Ig G), and lysozyme (Lys)

domains. All the five functional domains of AIB1, bHLH/PAS, S/T, RID, CID, and HAT, tagged with flag, were expressed and immunoprecipitated. Confocal imaging results showed that selected aptamer AY-3 can strongly bind with AIB1-CID as well as AIB1-S/T. In contrast, negligible binding against RID and HAT domains was observed (Fig. 4a).

To test whether aptamer AY-3 is able to recognize full-length AIB1 protein, flag-tagged AIB1 and the other members of the p160 family, SRC-1 and SRC-2, were

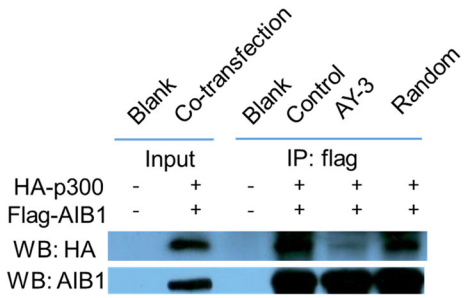

Fig. 5 Co-immunoprecipitation (CO-IP) analysis of AIB1-p300 interaction. Input: Total protein of transfected cell lysate. IP: flag: Protein in transfected cell lysate immunoprecipitated with flag M2 beads

expressed and immunoprecipitated by flag M2 beads. Thrombin, Immune Globulin G (Ig G), and lysozyme (Lys) were used as control groups. Aptamer AY-3 could bind with target protein AIB1 and also with its homologous proteins, SRC-1 and SRC-2. It was reported that the CBP/p300 interaction domain (CID) of the other two members of the p160 family, SRC-1 and SRC-2, with 58 and 44 % homology to AIB1-CID, has biological functions similar to those of AIB1-CID.(Chen et al. 1997) In contrast, no binding was observed for the control proteins (thrombin, IgG, and Lys) (Fig. 4b).

Selected Aptamer Can Reduce the Interaction Between AIB1 and p300

AIB1 functioned as a transcriptional coactivator by recruiting the acetyltransferase p300 on CID. As the selected aptamer AY-3 binds to AIB1-CID with high affinity, we speculated that the aptamer could reduce the interaction between AIB1 and p300. To test this hypothesis, human p300-tagged HA and AIB1-tagged flag were constructed into the mammalian expression vector and co-expressed in 293T cells. The co-immunoprecipitation result showed that the flag antibody could precipitate with p300 protein in the control group and with random sequence in the co-immunoprecipitation mixture (Fig. 5). In contrast, with AY-3 treatment, the precipitated p300 was dramatically downregulated, indicating that AY-3 interfered with the interaction between AIB1 and p300. We considered that the reduction of interaction between AIB1 and p300 was caused by competitive binding of selected aptamer AY-3 to AIB1-CID.

Conclusion

It has been shown that AIB1 is overexpressed in multiple human cancers and plays an important role in tumorigenesis. As a cancer-amplified coactivator, AIB1 promotes cancer progression by enhancing several oncogenic pathways. Because of its intrinsic advantages, aptamers with the ability to inhibit AIB1 transactivation function may be potential therapeutic agents applicable for AIB1 overexpressed cancers. After twelve rounds of selection using recombinant flag-AIB1-CID protein as target (highly significant for AIB1 recruiting protein p300), we identified several single-stranded DNA sequences that selectively bind to flag-AIB1-CID. Among them, aptamer AY-3 was demonstrated to recognize p160 coactivator family proteins specifically. The results revealed that AY-3 could bind to both CID and S/T domain of AIB1 protein. Moreover, CO-immunoprecipitation analysis proved that the function of AIB1 recruiting p300 was restrained by AY-3, implying that this aptamer has great potential for further development of novel therapeutic agents for the treatment of AIB1 overexpressed cancer.

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References

Anzick SL, Kononen J, Walker RL, Azorsa DO, Tanner MM, Guan XY, Sauter G, Kallioniemi OP, Trent JM, Meltzer PS (1997) AIB1, a steroid receptor coactivator amplified in breast and ovarian cancer. Science 277:965–968

Chen H, Lin RJ, Schiltz RL, Chakravarti D, Nash A, Nagy L, Privalsky ML, Nakatani Y, Evans RM (1997) Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300. Cell 90:569–580

Fang X, Tan W (2010) Aptamers generated from cell-SELEX for molecular medicine: a chemical biology approach. Acc Chem Res 43:48–57

Guan XY, Meltzer PS, Dalton WS, Trent JM (1994) Identification of cryptic sites of DNA sequence amplification in human breast cancer by chromosome microdissection. Nat Genet 8:155–161

Hu J, Wu J, Li C, Zhu L, Zhang WY, Kong G, Lu Z, Yang CJ (2011) A G-quadruplex aptamer inhibits the phosphatase activity of oncogenic protein Shp2 in vitro. ChemBioChem 12:424–430

Jayasena SD (1999) Aptamers: an emerging class of molecules that rival antibodies in diagnostics. Clin Chem 45:1628–1650

Kishimoto H, Wang Z, Bhat-Nakshatri P, Chang D, Clarke R, Nakshatri H (2005) The p160 family coactivators regulate breast cancer cell proliferation and invasion through autocrine/paracrine activity of SDF-1alpha/CXCL12. Carcinogenesis 26:1706–1715

Li J, O'Malley BW, Wong J (2000) p300 requires its histone acetyltransferase activity and SRC-1 interaction domain to facilitate thyroid hormone receptor activation in chromatin. Mol Cell Biol 20:2031–2042

Liao L, Kuang SQ, Yuan Y, Gonzalez SM, O'Malley BW, Xu J (2002) Molecular structure and biological function of the cancer-amplified nuclear receptor coactivator SRC-3/AIB1. J Steroid Biochem Mol Biol 83:3–14

Litterst CM, Pfitzner E (2001) Transcriptional activation by STAT6 requires the direct interaction with NCoA-1. J Biol Chem 276:45713–45721

Liu Z, Wong J, Tsai SY, Tsai MJ, O'Malley BW (1999) Steroid receptor coactivator-1 (SRC-1) enhances ligand-dependent and receptor-dependent cell-free transcription of chromatin. Proc Natl Acad Sci USA 96:9485–9490

Liu Z, Wong J, Tsai SY, Tsai MJ, O'Malley BW (2001) Sequential recruitment of steroid receptor coactivator-1 (SRC-1) and p300 enhances progesterone receptor-dependent initiation and reinitiation of transcription from chromatin. Proc Natl Acad Sci USA 98:12426–12431

Long W, Yi P, Amazit L, LaMarca HL, Ashcroft F, Kumar R, Mancini MA, Tsai SY, Tsai MJ, O'Malley BW (2010) SRC-3Delta4 mediates the interaction of EGFR with FAK to promote cell migration. Mol Cell 37:321–332

Long W, Foulds CE, Qin J, Liu J, Ding C, Lonard DM, Solis LM, Wistuba II, Tsai SY, Tsai MJ et al (2012) ERK3 signals through SRC-3 coactivator to promote human lung cancer cell invasion. J Clin Invest 122:1869–1880

Louie MC, Zou JX, Rabinovich A, Chen HW (2004) ACTR/AIB1 functions as an E2F1 coactivator to promote breast cancer cell proliferation and antiestrogen resistance. Mol Cell Biol 24:5157–5171

Mo P, Zhou Q, Guan L, Wang Y, Wang W, Miao M, Tong Z, Li M, Majaz S, Liu Y et al (2015) Amplified in breast cancer 1 promotes colorectal cancer progression through enhancing notch signaling. Oncogene 34:3935–3945

Nutiu R, Li Y (2005) In vitro selection of structure-switching signaling aptamers. Angew Chem Int Ed Engl 44:1061–1065

Osborne SE, Ellington AD (1997) Nucleic acid selection and the challenge of combinatorial chemistry. Chem Rev 97:349–370

Planas-Silva MD, Shang Y, Donaher JL, Brown M, Weinberg RA (2001) AIB1 enhances estrogen-dependent induction of cyclin D1 expression. Cancer Res 61:3858–3862

Rosenberg JE, Bambury RM, Van Allen EM, Drabkin HA, Lara PN Jr, Harzstark AL, Wagle N, Figlin RA, Smith GW, Garraway LA et al (2014) A phase II trial of AS1411 (a novel nucleolin-targeted DNA aptamer) in metastatic renal cell carcinoma. Invest New Drugs 32:178–187

Shangguan D, Tang Z, Mallikaratchy P, Xiao Z, Tan W (2007) Optimization and modifications of aptamers selected from live cancer cell lines. ChemBioChem 8:603–606

Soundararajan S, Chen W, Spicer EK, Courtenay-Luck N, Fernandes DJ (2008) The nucleolin targeting aptamer AS1411 destabilizes Bcl-2 messenger RNA in human breast cancer cells. Cancer Res 68:2358–2365

Suen CS, Berrodin TJ, Mastroeni R, Cheskis BJ, Lyttle CR, Frail DE (1998) A transcriptional coactivator, steroid receptor coactivator-3, selectively augments steroid receptor transcriptional activity. J Biol Chem 273:27645–27653

Tien JC, Xu J (2012) Steroid receptor coactivator-3 as a potential molecular target for cancer therapy. Expert Opin Ther Targets 16:1085–1096

Tuerk C, Gold L (1990) Systematic evolution of ligands by exponential enrichment: RNA ligands to bacteriophage T4 DNA polymerase. Science 249:505–510

Voegel JJ, Heine MJ, Tini M, Vivat V, Chambon P, Gronemeyer H (1998) The coactivator TIF2 contains three nuclear receptor-binding motifs and mediates transactivation through CBP binding-dependent and -independent pathways. EMBO J 17:507–519

Wilson DS, Szostak JW (1999) In vitro selection of functional nucleic acids. Annu Rev Biochem 68:611–647

Wu RC, Qin J, Hashimoto Y, Wong J, Xu J, Tsai SY, Tsai MJ, O'Malley BW (2002) Regulation of SRC-3 (pCIP/ACTR/AIB-1/RAC-3/TRAM-1) coactivator activity by I kappa B kinase. Mol Cell Biol 22:3549–3561

Wu C, Yan L, Wang C, Lin H, Chen X, Yang CJ (2010) A general excimer signaling approach for aptamer sensors. Biosens Bioelectron 25:2232–2237

Xie D, Sham J, Zeng WF, Lin HL, Bi J, Che LH et al (2005) Correlation of AIB1 over-expression with advanced clinical stage of human colorectal carcinoma. Hum Pathol 36:777–783

Xu Y, Chen Q, Li W, Su X, Chen T, Liu Y, Zhao Y, Yu C (2010) Overexpression of transcriptional coactivator AIB1 promotes hepatocellular carcinoma progression by enhancing cell proliferation and invasiveness. Oncogene 29:3386–3397

Yan AC, Bell KM, Breeden MM, Ellington AD (2005) Aptamers: prospects in therapeutics and biomedicine. Front Biosci 10:1802–1827

Yan J, Tsai SY, Tsai MJ (2006a) SRC-3/AIB1: transcriptional coactivator in oncogenesis. Acta Pharmacol Sin 27:387–394

Yan J, Yu CT, Ozen M, Ittmann M, Tsai SY, Tsai MJ (2006b) Steroid receptor coactivator-3 and activator protein-1 coordinately regulate the transcription of components of the insulin-like growth factor/AKT signaling pathway. Cancer Res 66:11039–11046

Zhou HJ, Yan J, Luo W, Ayala G, Lin SH, Erdem H, Ittmann M, Tsai SY, Tsai MJ (2005) SRC-3 is required for prostate cancer cell proliferation and survival. Cancer Res 65:7976–7983