Priority Report

A Specific STAT3-Binding Peptide Exerts Antiproliferative Effects and Antitumor Activity by Inhibiting STAT3 Phosphorylation and Signaling

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Abstract

STAT3 promotes the survival, proliferation, metastasis, immune escape, and drug resistance of cancer cells, making its targeting an appealing prospect. However, although multiple inhibitors of STAT3 and its regulatory or effector pathway elements have been developed, bioactive agents have been somewhat elusive. In this report, we report the identification of a specific STAT3-binding peptide (APTSTAT3) through phage display of a novel “aptide” library. APTSTAT3 bound STAT3 with high specificity and affinity (∼231 nmol/L). Addition of a cell-penetrating motif to the peptide to yield APTSTAT3-9R enabled uptake by murine B16F1 melanoma cells. Treatment of various types of cancer cells with APTSTAT3-9R blocked STAT3 phosphorylation and reduced expression of STAT targets, including cyclin D1, Bcl-xL, and survivin. As a result, APTSTAT3-9R suppressed the viability and proliferation of cancer cells. Furthermore, intratumoral injection of APTSTAT3-9R exerted potent antitumor activity in both xenograft and allograft tumor models. Our results offer a preclinical proof-of-concept for APTSTAT3 as a tractable agent for translation to target the broad array of cancers harboring constitutively activated STAT3. Cancer Res; 74(8); 1–8. ©2014 AACR.

Introduction

STAT3, a member of the STAT family, has received considerable attention for the important role it plays in signaling pathways linked to inflammation-associated diseases and cancers (1). Notably, unlike the transient activation of STAT3 characteristic of normal cells, STAT3 tends to be constitutively activated in most cancer cells. In these cells, STAT3 is associated with tumorigenesis and malignancy because its downstream signaling results in production of a number of cytokines that regulate proliferation, angiogenesis, survival, and metastasis (2). For these reasons, many research groups have focused on developing inhibitors that can block upstream or downstream elements in the STAT3 signaling pathway (3, 4). Upon activation, STAT3 becomes phosphorylated and undergoes dimerization. The active, dimeric form enters the nucleus, in which it binds to target DNA-response elements, leading to the expression of proteins related to cancer progression and malignancy. Thus, inhibitors reported to date, including small molecules (5–9), decoy oligodeoxynucleotides (ODN; ref. 10), siRNAs (11), and peptides (12, 13) and their peptidomimetics (14, 15), target one of the key steps required for STAT3-mediated gene expression. Several small molecules that can inhibit phosphorylation and subsequent dimerization by binding to the SH2 domain of STAT3 have been shown to suppress cancer cell growth in vitro and reduce tumor burden in vivo, and indeed a few such inhibitors are now in various phases of clinical trials (3). Decoy ODNs that can intercept the active form of the STAT3 dimer also show potential as inhibitors in in vivo tumor models (16).

Peptide-based STAT3 inhibitors have also been reported. These inhibitory phospho-peptides (P’YLKTK, Y’LPQTV), based on a truncated gp130 sequence, bind to the SH2 domain of STAT3 and block dimerization (17, 18). However, the relatively low potency and limited cell permeability of such phospho-peptides have hampered their further use in an in vivo setting. Peptide libraries have been screened for interaction with the DNA-binding domain (DBD) of STAT3, and the identified peptides have been shown to inhibit STAT3 DNA-binding activity (19). Very recently, a short peptide derived from the helices of the N-terminal domain of STAT3 has been shown to inhibit STAT3 transcriptional activity (20). However, although these peptide inhibitors have shown cytotoxicity in various cancer cells by blocking STAT3 signaling, to date there have been few reports demonstrating antitumor efficacy in vivo (3, 21).

Aptides, developed by our laboratory, constitute a platform technology that enables screening and identification of high-affinity and specificity peptides for various biologic targets (22). An aptide consists of a tryptophan zipper scaffold that forms a robust β-hairpin structure and a target-binding site containing...
12 randomizable amino acids that enables library construction (Fig. 1A). Phage display of an aptide library has enabled us to identify a number of aptides specific to various protein targets (22). Most such aptides showed affinities in the tens of nanomolar range, even before affinity maturation, and as such represent a general source of high-affinity binders. Here, we report the screening and identification of a STAT3-specific aptide (APTSTAT3) and evaluate its potential as an inhibitor of STAT3 signaling in cancer cells in vitro and in tumor-bearing mice in vivo. To the best of our knowledge, APTSTAT3 is the first reported peptide inhibitor to show therapeutic efficacy in in vivo animal models by blocking STAT3 activation.

Materials and Methods

Cell lines and culture

The A549 human lung carcinoma, B16F1 mouse melanoma, HepG2 human hepatocellular carcinoma, MDA-MB-231 breast cancers, and U87MG human neuronal glioblastoma cells were obtained from the American Type Culture Collection. A549 cells were maintained in Ham F12K. B16F1 and MDA-MB-231 cells were maintained in RPMI-1640 medium. HepG2 cells were maintained in Dulbecco’s Modified Eagle Medium. U87MG cells were maintained in Minimum Essential Medium. The cell culture media were supplemented with 10% heat-inactivated FBS.

Materials

All peptides, including APTSTAT3-9R and APRscr-9R, were custom synthesized by AnyGen. Antibodies against STAT3, STAT1, STAT5, phosphorylated STAT3 (P-STAT3), P-STAT5, P-STAT1 AKT, P-AKT, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), Bcl-xL, survivin, and cyclin D1 were obtained from Cell Signaling Technology.

Figure 1. Characterization of APTSTAT3, a specific STAT3-binding peptide. A, schematic depiction of the structure of a STAT3-specific aptide (APTSTAT3) and control scrambled peptide (APTscr) with amino acid sequences and a cell permeable form of the STAT3-specific aptide (APTSTAT3-9R). B, phage ELISAs using a phage displaying APTSTAT3 sequence against various proteins (STAT3, streptavidin, BSA, VEGF, TNF-α, and anti-His6-tag-antibody; left). C, concentration-escalation ELISAs using APTSTAT3, APTSTAT3-9R, and APTscr-9R peptides against STAT3 protein. Antiaptide (trpzip) mAb was used to detect. D, confocal microscopy images of A549 human lung carcinoma cells after treatment with none (control), FITC-APTSTAT3-9R, and FITC-APTscr-9R.

APTSTAT3: HGFQWPSSWTVENKWTWKAGYQFLK
APTscr: HASDRNSWTVENKWTWKGLHEQSD
Screening and identification of STAT3-specific binders

A STAT3-specific aptide was identified using a phage display-based screening method, as described previously (22). Briefly, STAT3 was immobilized on 96-well plates (Corning) overnight at 4°C. After incubating phage library pools on STAT3-immobilized plates for 1 hour at 25°C, unbound phages were removed by washing with PBS containing 0.5% Tween-20 (PBS-T), and bound phages were eluted with 0.2 mol/L glycine buffer (pH 2.2), followed by immediate neutralization with Tris-HCl (pH 8.8). The eluted phages were amplified using log-phase cultures of Escherichia coli ER2537 (New England Biolabs). The above mentioned screening steps were iterated for phosphatase (HRP)-conjugated anti-M13 antibody (GE Healthcare) followed by monitoring absorbance at 450 nm after incubation with the chromogenic substrate tetramethylbenzidine.

DNA-binding assay

Following treatment of cells with APTSTAT3-9R, APRscr-9R, or PBS for 6 hours, cell extracts were prepared and analyzed for STAT3 DNA-binding activity in triplicate using a TransAM STAT3 Transcription Factor Assay Kit, following the manufacturer’s protocol (Active Motif).

Quantitative reverse transcription-PCR

Total RNA was isolated using Ribo EX (GeneAll) and subjected for reverse transcription using Reverse Transcriptase (Promega) according to the manufacturer’s instructions. Quantitative real-time PCR were carried out as described previously (23).

Western blot analysis

Cell lysates were prepared in PRO-PREP protein extraction solution. Protein concentrations were determined by Bradford assay. A sample of 30 μg of each protein was loaded in 15% SDS–PAGE gels. After gel electrophoresis, proteins were transferred to polyvinylidene difluoride membrane (Millipore). The membranes were blocked in 5% bovine serum albumen (BSA) in TBS containing 0.1% Tween 20 at room temperature for 2 hours followed by overnight incubation at 4°C with primary antibodies in TBST containing 5% BSA. The membranes were then incubated with HRP-conjugated secondary antibody in TBST containing 5% BSA for 30 minutes at room temperature. Anti-mouse and -rabbit antibody were obtained from Santa Cruz Biotechnology. Specific proteins were detected by ChemiDoc (Bio-Rad).

Cell viability assay

Cells were plated in a 96-well plate (5,000 cells/well) and incubated for 12 hours. After incubation the cells were treated with nine-arginine (9R), APTSTAT3-9R, and APRscr-9R for 12 hours. After 12 hours incubation, 20 μL MTT (5 mg/mL) was added to each well. After 4 hours, 100 μL dimethyl sulfoxide was added to each well, and absorbance was measured at 570 nm using a Spectra Maxplus microplate reader (Molecular Devices).

Colony formation assay

Cells in growth medium were cultured at 500 cells per well in 12-well plates and treated with APTSTAT3-9R, APRscr-9R, or PBS on the following day. Cells were then allowed to grow for 2 weeks until colonies were visible. Colonies were stained by incubating with 0.1% Coomassie Brilliant Blue R-250 for 20 minutes.

Flow cytometry analysis

The Annexin V–fluorescein isothiocyanate (FITC) Apoptosis Detection Kit (BD Biosciences) was used to detect apoptosis by flow cytometry. Cells were exposed to APTSTAT3-9R, APRscr-9R, or PBS treatment at 30 μmol/L, and after 6 hours, they were harvested (including detached cells), and processed according to the manufacturer’s instructions.

Antitumor efficacy in the A549 xenograft tumor model

A549 cells (1 × 10⁷ cells) were harvested and resuspended in 50 μL F12K media and injected subcutaneously into the right flank of 6-week-old female BALB/c nude mice. Approximately 14 days later, when tumor volumes had reached approximately 50 mm³, the mice were randomly divided into three groups (n = 5 mice/group): APTSTAT3-9R, APRscr-9R, and PBS. Mice were intratumorally injected four times with APTSTAT3-9R and APRscr-9R (8 mg/kg in 50 μL PBS) or PBS. At the same time, tumor volume was determined by measuring with calipers and calculated according to the formula, A × B² × 0.5, where A is the longest dimension of the tumor and B is the shortest dimension of the tumor. After 30 days, mice were sacrificed and tumors were excised for use in other assays. All mice were maintained at an animal facility under pathogen-free conditions. Experimental procedures and handling of mice were carried out in accordance with experimental animal guidelines approved by our Institutional Animal Care and Use Committee.

Statistical analysis

The statistical significance of differences among groups was calculated by one-way ANOVA. A P value of < 0.001 was considered statistically significant.

Results and Discussion

A specific STAT3-binding peptide and its cell permeable derivative

Using phage display of an aptide library, we were able to screen and identify a specific STAT3-binding peptide (Fig. 1A). A total of four rounds of selection were performed to enrich for phage clones that showed specificity for STAT3 in phage ELISAs (Supplementary Fig. S1). Sequencing of the bound phages yielded only an aptide sequence. The affinity and specificity of the identified STAT3-binding aptide (APTSTAT3) were measured. A surface plasmon resonance assay revealed that APTSTAT3 bound to STAT3 with a dissociation constant (Kd) of 231 nmol/L; a control peptide containing the same trpzip scaffold but with a scrambled sequence in the target-binding site, APTscr, did not bind STAT3 (Supplementary Fig. S2). Phage ELISAs showed that the phage
displaying APT STAT3 sequence was highly specific to the target STAT3 compared with other proteins, whereas the phage displaying APTscr sequence showed no appreciable binding to any of the proteins tested (Fig. 1B). To impart cell permeability to APT STAT3, we fused APT STAT3 with a 9R, a cell-penetrating peptide (Fig. 1A; ref. 24). ELISAs using an anti-aptide monoclonal antibody (mAb) showed that APT STAT3–9R was also able to specifically bind STAT3 with a comparable binding ability to APT STAT3, as evidenced by a concentration-dependent increase in the ELISA signal, whereas the 9R-modified scrambled aptide (APTscr–9R) showed little signal enhancement (Fig. 1C). Next, we examined whether the attachment of 9R to the aptides would enable cell penetration and, thus, intracellular localization. As clearly shown in Fig. 1D, most B16F1 melanoma cells treated with FITC-labeled APT STAT3–9R or APTscr–9R showed intense fluorescence signals in the cytosol, demonstrating cellular uptake and confirming the cell-penetrating ability of the 9R-conjugated aptides.

APT STAT3–9R inhibits STAT3 activation and downstream signaling by specifically blocking STAT3 phosphorylation

To examine whether binding of APT STAT3–9R to STAT3 is able to affect STAT3-mediated signaling pathway, we carried out STAT3–DNA-binding assays. Human lung carcinoma cells (A549) were chosen because they are known to maintain high levels of constitutively activated STAT3 (1). The cells were treated with various concentrations of APT STAT3–9R (7.5, 15, and 30 μmol/L) or APTscr–9R (30 μmol/L) for 6 hours and then DNA-binding activity of the activated STAT3 dimer existing in the cell extracts was measured using a STAT3 Transcription Factor Assay Kit (see Supplementary Information). APT STAT3–9R significantly reduced STAT3–DNA-binding activity in a dose-dependent manner, whereas APTscr–9R even at a concentration of 30 μmol/L did not affect STAT3–DNA-binding activity in A549 cells (Fig. 2A). This result suggests that APT STAT3 is not a just binder but an effector involved in inhibition of homo- or heterodimerization of P-STAT3.

Figure 2. The inhibitory effects of APT STAT3–9R on STAT3 signaling. A, DNA-binding assay for STAT3 in cell extracts of A549 human lung carcinoma following treatment with APT STAT3–9R (7.5, 15, and 30 μmol/L) or APTscr–9R (30 μmol/L) for 6 hours. B, quantification of mRNA level of STAT3 downstream target genes, including Bcl-xL, cyclin D1, and survivin, in A549 cells following treatment with APT STAT3–9R (7.5, 15, and 30 μmol/L) or APTscr–9R (30 μmol/L) for 6 hours. C, dose-dependent Western blot assays for STAT3 downstream target proteins (Bcl-xL, cyclin D1, and survivin) and P-STAT3 (Y705) in A549 cells following treatment with APT STAT3–9R (7.5, 15, and 30 μmol/L) or APTscr–9R (30 μmol/L) for 6 hours. D, Western blot assays for STAT3, P-STAT3 (Y705), and other signaling in A549 cells following treatment with APT STAT3–9R and APTscr–9R (30 μmol/L) for 6 hours. *, P < 0.005 (one-way ANOVA); **, P < 0.001.
further examine the inhibitory effect of APTSTAT3-9R on STAT3 downstream signaling, we measured mRNA expression of the STAT3 target genes, cyclin D1, Bcl-xL, and survivin (10), by quantitative reverse transcription-PCR. Treatment with APTSTAT3-9R decreased the mRNA levels of the indicated targets in a dose-dependent manner in A549 cells, whereas APTscr-9R (30 μmol/L) treatment had little effect (Fig. 2B). Next, we estimated the expression of these genes at the protein level by Western blotting after treatments of A549 cells with APTSTAT3-9R (7.5, 15, and 30 μmol/L) or APTscr-9R (30 μmol/L) for 6 hours. As shown in Fig. 2C, the expression level of each protein was markedly decreased by treatment with APTSTAT3-9R in a dose-dependent manner compared with that in untreated controls. As expected, cells treated with nonrelevant APTscr-9R showed no appreciable difference in the levels of these proteins compared with controls. Furthermore, a similar trend of results was also obtained in various murine and human cancer cell lines, including B16F1, HepG2, MDA-MB-231, and U87MG that are known to express constitutively activated STAT3, confirming the inhibitory effect of APTSTAT3-9R on STAT3 downstream signaling (Supplementary Figs. S3–S5). Interestingly, we found that APTSTAT3-9R effectively inhibited phosphorylation of STAT3 (Fig. 2D) but did not affect the level of AKT phosphorylation, indicating specificity of the aptide. This suggests that APTSTAT3-9R may be able to suppress expression of STAT3-associated target genes by specifically inhibiting STAT3 phosphorylation.

On one hand, there are other proteins belonging to STAT family, some of which have some degree of sequence homology to STAT3. Thus, we further examined the specificity of APTSTAT3 over other STATs. Phage ELISAs using a phage displaying APTSTAT3 sequence against STAT3, STAT1, and STAT5 revealed preferential binding of the aptide phage to the target STAT3 over STAT1 or STAT5 (Supplementary Fig. S6A). Furthermore, as shown in the Western blot analysis data in A549 cells following treatment with APTSTAT3-9R or APTscr-9R (30 μmol/L; Supplementary Fig. S6B), APTSTAT3-9R significantly inhibited only STAT3 phosphorylation but did not affect phosphorylation of other STAT1 and STAT5, indicating high specificity of the STAT3 aptide. On the other hand, it is known that the SH2 domain of STAT3 plays a key role in membrane recruitment, recognition of the phosphorylated site, and subsequent homodimerization of P-STAT3 (7, 21). To elucidate the binding site of APTSTAT3 in STAT3, we carried out binding assays using phage ELISAs for STAT3 and its domains: DBD, SH2 domain, and transactivation domain (TA). A phage displaying APTSTAT3 sequence showed much higher binding to SH2 domain than other domains (TA and DBD), which was close to the level of binding to parent STAT3; however, moderate binding to DBD was also observed (Supplementary Fig. S7A). This finding suggests that the SH2 domain may be a putative binding site of the aptide. Furthermore, to obtain a piece of clues about the mode-of-action of APTSTAT3, we carried out a Jak2 kinase activity assay as the kinase is a key enzyme responsible for STAT phosphorylation. As illustrated in Supplementary Fig. S7B and S7C, phosphorylation of the plate-immobilized STAT3 by Jak2 was significantly inhibited with increasing amounts of APTSTAT3-9R, whereas the control scrambled peptide minimally affected the Jak2 activity. Although more studies such as the X-ray crystallographic study on the STAT3–APTSTAT3 complex are required to probe the exact binding site and the mode-of-action of APTSTAT3, we speculate that tight binding of APTSTAT3 to the SH2 domain may inhibit the interaction between STAT3 and JAK2 during the membrane recruitment step, thereby causing inhibition of STAT3 phosphorylation.

**APTSTAT3-9R suppresses cell viability and proliferation of cancer cells**

To examine whether the inhibitory effect of APTSTAT3-9R on STAT3 signaling affects cancer cell viability, we performed MTT assays. The IC_{50} value of APTSTAT3-9R was estimated to be 10 to 20 μmol/L in A549 cells; in contrast, those of APTscr-9R and 9R alone were estimated to be >100 μmol/L (Fig. 3A). A similar level of IC_{50} values was attained in B16F1 and HepG2 cells treated with APTSTAT3-9R (Supplementary Figs. S3D and S4C). In addition, we carried out colony formation assay to assess whether APTSTAT3-9R suppresses cancer cell proliferation. Proliferation of A549 and B16F1 cancer cells was monitored for 2 weeks after cell seeding (500 cells/well) in the presence of APTSTAT3-9R or APTscr-9R (30 μmol/L). Colony formation was significantly suppressed in the APTSTAT3-9R–treated group but not in the APTscr-9R group (Fig. 3B and Supplementary Fig. S3E). Furthermore, we confirmed that APTSTAT3-9R treatment induced apoptosis of A549 cells by approximately 3-fold increase compared with APTscr-9R in flow cytometry assessment (Fig. 3C). Collectively, these results indicate that APTSTAT3-9R effectively suppresses cell survival and growth.

**APTSTAT3-9R suppresses tumor growth in vivo**

Encouraged by the potency of APTSTAT3-9R in inhibiting cell proliferation in vitro, we explored the antitumor efficacy of the aptide in vivo. A human lung carcinoma xenograft model was prepared by subcutaneous implantation of A549 cancer cells. After tumors had reached a volume of approximately 50 mm³ (2 weeks), APTSTAT3-9R or APTscr-9R (8 mg/kg) was intratumorally injected every other day for a total of four injections. Tumor burden was significantly reduced (−65% relative to the control) in the APTSTAT3-9R–treated group (Fig. 4A) compared with that in the PBS control group; however, there was little difference in tumor size between APTscr-9R and PBS groups. Images of excised tumors at day 30 further indicate significant difference between the aptide-treated group and control groups (Fig. 4B). We found that the amount of P-STAT3 in the excised tumor tissues of the APTSTAT3-9R–treated group was substantially diminished, whereas APTscr-9R did not show any appreciable inhibition of STAT3 phosphorylation in the tumor tissues (Fig. 4C). Furthermore, TUNEL (terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling) assays on excised tumor tissues revealed that, unlike PBS or the scrambled aptide–treated groups, the APTSTAT3-9R–treated group showed a significant level of apoptosis in tumor sections, presumably due to inhibition of STAT3 activation and downstream signaling (Fig. 4D). In addition to the A549 xenograft mouse model,
we also evaluated the anticancer efficacy of APTSTAT3-9R in two additional tumor models, B16F1 melanoma allograft and U87MG glioblastoma xenograft models. Because B16F1 melanoma tumor is known to be aggressive and rapidly grows, APTSTAT3-9R was injected to the same foot pad in which the melanoma cells were implanted 2 days ago as suggested in the protocol published elsewhere (25). The APTSTAT3-9R substantially reduced tumor burden by approximately 49% and, thus, extended survival time by more than 15 days compared with the control (PBS-treated) group (Supplementary Fig. S8). In the case of the U87MG glioblastoma xenograft tumor model the first intratumoral injection of each group was initiated when the tumor volumes had reached approximately 120 mm³ and terminated after a total of four times injection. The tumor growth was significantly inhibited by treatment of the STAT3-specific aptide but little inhibition was seen from the scrambled aptide–treated group (∼45% vs. ∼7% inhibition; Supplementary Fig. S9). Collectively, these results indicate that APTSTAT3-9R could effectively suppress tumor growth in the

**Figure 3.** The inhibitory effects of APTSTAT3-9R on cell viability and proliferation in A549 human lung carcinoma. A, cytotoxicity of APTSTAT3-9R, APTscr-9R, and 9R toward A549 human lung carcinoma cells following treatment with each peptide for 12 hours, measured by the MTT assay. Cell viability was expressed as a percentage (Means ± SD; n = 5) relative to the control (100%). B, anchorage-independent proliferation of A549 cells following treatment with APTSTAT3-9R or APTscr-9R (30 μmol/L), as determined by colony-forming assays. Colonies were stained with Coomassie blue. C, apoptosis of A549 cells treated with APTSTAT3-9R or APTscr-9R (30 μmol/L) for 6 hours was assessed by using flow cytometry. Annexin V–FITC and propidium iodide (PI) staining were denoted in x- and y-axis, respectively. The number represents the percentage of apoptotic cells (upper right quadrant).

**Conclusion**

In summary, we screened and identified a specific STAT3-binding peptide (APTSTAT3) using aptide platform technology. With the addition of a cell-penetrating motif, the resulting APTSTAT3-9R aptide was able to suppress the viability and proliferation of cancer cells by blocking STAT3 phosphorylation, thereby inhibiting STAT3 downstream signaling. Furthermore, intratumorally injected APTSTAT3-9R showed potent antitumor activity in both xenograft and allograft tumor models. To the best of our knowledge, APTSTAT3-9R is the first example of a peptide-based STAT3 inhibitor demonstrating potent antitumor efficacy *in vivo*. Taken together, these findings suggest that APTSTAT3 holds potential for the treatment of cancers maintaining high level of constitutively activated STAT3. Further works are currently undergoing to examine the suitability of APTSTAT3-9R for clinical applications.

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the feasibility of the aptide in treating STAT3-associated inflammation diseases.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D. Kim, I.-H. Lee, S. Jon
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Kim, M. Choi, H. Kim, S. Ahn, P.E. Saw, H. Jeon, Y. Lee
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D. Kim, M. Choi, H. Kim, S. Ahn, H. Jeon, Y. Lee, S. Jon

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