Targeted Radiotherapy for Prostate Cancer with an Oncolytic Adenovirus Coding for Human Sodium Iodide Symporter

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Abstract

Purpose: Oncolytic adenoviruses are promising tools for cancer therapy. Although several clinical reports have indicated both safety and promising antitumor capabilities for these viruses, there are only a few examples of complete tumor eradication. Thus, the antitumor efficacy of oncolytic adenoviruses needs to be improved. One potentially useful approach is combination with radiotherapy.

Experimental Design: To target systemically administered radioiodide to tumors, we created Ad5/3-Δ24-human sodium iodide symporter (hNIS), a Rb-p16 pathway selective infectivity enhanced oncolytic adenovirus encoding hNIS.

Results: Ad5/3-Δ24-hNIS replication effectively killed prostate cancer cells in vitro and in vivo. Also, the virus-mediated radioiodide uptake into prostate cancer cells in vitro and into tumors in vivo. Furthermore, Ad5/3-Δ24-hNIS with radioiodide was significantly more effective than virus alone in mice with prostate cancer xenografts.

Conclusions: These results suggest that oncolytic adenovirus-mediated targeted radiotherapy might be a potentially useful option for enhancing the efficacy or oncoviral virotherapy. (Clin Cancer Res 2009;15(17):5396–403)

Prostate cancer is the most common cancer in the male population and the second leading cause of cancer deaths in western men. Although radiation therapy and surgery can cure many patients, and watchful waiting is an option for some, >30% of treated patients relapse. For disseminated or recurrent disease, androgen ablation therapies are often initially effective, but emergence of androgen-independent locally recurrent or distant disease is usually fatal. Therefore, there is a need for developing new antitumor approaches for androgen-independent prostate cancer. The main target for prostate cancer metastasis is bone, but dissemination to lung and liver is also common (1). Although prostate cancer metastases are not insensitive to radiation therapy, relatively high radiation doses are needed. In the context of local disease, this can be achieved with external beam radiation therapy or brachytherapy. However, side effects increase with field size; therefore, treatment of disseminated disease with external beam radiation results in only palliation because a lower dose must be used. Thus, it would be useful if radiation could be targeted to tumors only.

Adenoviruses are the most commonly used vectors for cancer gene therapy. Oncolytic adenoviruses, which can destroy target cells via viral replication (2), are promising tools for developing novel treatment modalities for cancer. Oncolytic Ad5-based viruses have shown efficacy and safety in preclinical (3–6) and clinical trials (7, 8), including the treatment of prostate cancer (9–11). However, variable expression of the primary Ad5 receptor, the coxsackie-adenovirus receptor, may limit the efficacy of Ad5-based constructs (12). Various approaches can be used to improve oncoviral transduction of cancer cells. For example, switching the Ad5 fiber knob to serotype 3 knob improves the transduction and enhances the cell-killing capacity of the virus in the context of many cancer types including prostate cancer (3, 6, 13, 14). Although several clinical reports have indicated promising antitumor capabilities with oncolytic viruses, there are only a few examples of complete tumor eradication. One possibility to improve therapeutic efficacy is to use the synergy of radiation and oncolytic adenoviruses (15–17). However, the systemic...
nature of disseminated prostate cancer calls for body-wide targeting of radiation to tumor cells. This might be achievable by incorporating the human sodium iodide symporter (hNIS) transgene into an oncolytic adenovirus. hNIS is an integral plasma membrane glycoprotein mainly expressed in thyroid follicular cells (18). The biological function of hNIS is to mediate active transport of iodine, which is a crucial component for thyroid hormone biosynthesis. This transporting ability of hNIS has already been used for clinical and preclinical imaging, including prostate cancer (31,32). We show that Ad5/3-Δ24-hNIS and pAd5/3-Δ24-luc1 using hNIS-specific primers (forward 5′-CTCTGGAACCGTGCTCAC-3′ and reverse 5′-TCCAAGATTAGCAGGTCTC-3′) and β-actin-specific primers (forward 5′-CGGAGCCCAGACGACGACA-3′ and reverse 5′-CAGCCGCTCTTCAATGTCAC-3′). PCR product size for hNIS and β-actin was 453 and 482 bp, respectively.

**Materials and Methods**

**Cell culture.** Androgen-independent prostate cancer cell lines 22Rv1, PC-3, and DU-145 and lung adenocarcinoma cell line A549 were purchased from the American Type Culture Collection. PC-3MM2 cells are a metastatic hormone-refractory subline of PC-3 (courtesy of Isaiah J. Fidler, M. D. Anderson Cancer Center). Human embryonic kidney epithelial 293 cells were purchased from Microbiex. Cell line 911 was obtained from Dr. Alex J. van der Eb (University of Leiden). All cell lines were cultured in the recommended conditions. Cell line samples. For both experiments, 10⁴ 293 cells were plated in 100 mm dishes in DMEM. They were freeze-thawed at -80°C and washed with 1× PBS 24 and 48 h post-infection and incubated with 7.4 kBq sodium iodide [¹²³I]NaI (MAP Medical Technologies Oy) for 20 min at room temperature. Cells were washed twice with 1× PBS followed by lysis using 300 μL Cell Culture Lysis Reagent for each sample (Promega). Radioactivity was quantified with a well counter connected to a multichannel analyzer Atomlab 950 (Biodex Medical System).

**Cell killing assays.** Prostate cancer cells were infected with Ad5/3-Δ24-hNIS and Ad5/3-Δ24-Dgp19K (10 VP/cell) for 2 h at 37°C. Cells were harvested 24 and 48 h after infection and incubated with 7.4 kBq sodium iodide [¹²³I]NaI (MAP Medical Technologies Oy) for 20 min at room temperature. Cells were washed twice with 1× PBS followed by lysis using 300 μL Cell Culture Lysis Reagent for each sample (Promega). Radioactivity was quantified with a well counter connected to a multichannel analyzer Atomlab 950 (Biodex Medical System).

**Reverse transcription-PCR.** Prostate cancer cells were infected with Ad5/3-Δ24-hNIS and Ad5/3-Δ24-Dgp19K (10 VP/cell) for 2 h at 37°C. Cells were harvested 24 and 48 h after infection and incubated with 7.4 kBq sodium iodide [¹²³I]NaI (MAP Medical Technologies Oy) for 20 min at room temperature. Cells were washed twice with 1× PBS followed by lysis using 300 μL Cell Culture Lysis Reagent for each sample (Promega). Radioactivity was quantified with a well counter connected to a multichannel analyzer Atomlab 950 (Biodex Medical System).

**TCID₅₀ assay**

**Cell line samples.** Prostate cancer cells (5 × 10⁴ per well) were plated in triplicates in 1 mL of 5% growth medium on 24-well plates, incubated overnight, and infected with Ad5/3-Δ24-hNIS (5 VP/cell) for 2 h at 37°C. At 8, 24, 48, and 72 h post-infection, cells and growth medium were collected, frozen at -80°C, and freeze-thawed three times. For TCID₅₀, the cells were spun down and the supernatant was added to 293 cells. **Tissue samples.** Organs collected from mice treated with Ad5/3- Δ24-hNIS and Ad5/3-Δ24-Dgp19K were collected, weighed, manually homogenized, and diluted into 800 μL DMEM. They were freeze-thawed at -80°C three times. For TCID₅₀, the tissue samples were spun down and the supernatant was added to 293 cells.

**Translational Relevance**

Treatment of metastatic solid tumors requires new approaches, as current therapeutic modalities cannot cure most cases. Expression of the human sodium iodide symporter as a transgene is an attractive strategy for targeting systemically applicable radioisotopes to tumors. Previous work has shown the utility of the approach for imaging. However, our article is the first study that combines a therapeutic radioiodide with an oncolytic adenovirus. This approach allows tumor cells to be killed due to the oncolytic effect of the virus and due to radiation-induced cell death and the approach also takes advantage of synergy between radiation and oncolytic adenovirus replication. These preclinical results facilitate clinical testing of the approach.
In vivo studies. Male NMRI/nude mice were purchased from Tacônic. Tumors were established in 8-week-old mice by subcutaneous injection of $5 \times 10^6$ PC-3-MM2 cells under medetomidine-ketamine-0.9% saline (1:2:7) anesthesia. In the imaging experiment, three mice received intratumorally saline (top left tumor), $7 \times 10^7$ VP Ad5/3-Δ24-Δgp19K (top right tumor), and $7 \times 10^7$ VP Ad5/3-Δ24-Δ24-hNIS (bottom right and left tumors) 11 and 12 days after tumor cell inoculation. A day after the last viral injection, mice received intravenously 1.85 MBq sodium iodide $[^{123}\text{I}]\text{NaI}$ (MAP Medical Technologies Oy) followed by imaging with $\gamma$-camera Toshiba 7200A/UI (Toshiba) 0.5, 1, 1.5, 2, 4, and 13 h after iodide exposure. Animal regulation did not allow analysis of later time points. The $\gamma$-energy peak 159 keV was recorded using 20% window, and 150 kilocounts were collected per image. The used matrix size was 256 $\times$ 256 $\times$ 16, and this made the pixel size 1.08 $\times$ 1.08 mm. At 13 h, various organs (heart, lung, liver, spleen, kidney, thyroid, stomach, muscle, blood, and bone) and tumors were collected, weighed, and analyzed with a well counter connected with a multichannel analyzer Atomlab 950 (Biodex Medical System). Results are expressed as percentage from initial iodide dose per gram of tissue.

For the therapeutic experiment, tumor-bearing mice were randomly divided into four groups (6 mice per group, 2 tumors per mouse): mock, $[^{131}\text{I}]\text{NaI}$, Ad5/3-Δ24-hNIS, and Ad5/3-Δ24-hNIS + $[^{131}\text{I}]\text{NaI}$. Six and 7 days after tumor cell inoculation, mice received intratumorally either growth medium or $7 \times 10^8$ VP Ad5/3-Δ24-Δ24-hNIS per tumor. A day after the last viral injection, mice received in intraperitoneally 50 MBq carrier-free sodium iodide $[^{123}\text{I}]\text{NaI}$ (MAP Medical Technologies Oy). Tumor size was measured every other day and the volume was calculated using the formula: length $\times$ width$^2$ $\times$ 0.5. When mice were killed due to tumor size, organs were collected and weighed and their radioactivity was determined with a $\gamma$-counter (Wizard 3; Perkin-Elmer) for 180 s. Results are expressed as percentage from initial iodide dose per gram of tissue.

Whole-body emitted radioactivity was measured at days 9, 10, 11, 13, 14, 15, and 17. On days 9 to 11, measurements were done on a dose calibrator (CRC-120; Capintec), and after day 11, measurements were done on a whole-body measurement apparatus consisting of a lead measurement chamber and a UniSpec tube-base multichannel analyzer with sodium iodide scintillation crystal (Canberra Industries). The mice were weighed at day 14, and the same weight was used in calculations throughout the experiment.

In all experiments, mice were killed when tumor size reached 15 mm in any diameter as required by animal regulations. The therapeutic in vivo experiment had to be stopped on day 17 due to animal husbandry constraints. All the animal experiments were approved by the National Committee for Animal Experimentation in Finland (State Provincial Office of Southern Finland).

Statistical analysis. Analysis of iodide uptake was done by one-way ANOVA with Bonferroni’s post hoc test. Analysis of tumor volume over time between experimental groups was done using a repeated-measures model with PROC MIXED (SAS version 9.1). The tumor volume measurements were log-transformed for normality. The a priori planned comparisons of specific differences in predicted treatment means averaged over time and at each time point by t statistics and Tukey-Kramer model were used for adjustments. For all analyses, a two-sided $P < 0.05$ was deemed statistically significant.

Results

hNIS-specific mRNA is detected in Ad5/3-Δ24-hNIS-infected prostate cancer cells. A new virus containing the Ad3 knob in the Ad5 fiber shaft, a 24-bp deletion in the E1A region, and hNIS inserted in the E3 was constructed (Fig. 1). To assess the expression of the transgene from the virus, hormone-refractory prostate cancer cell lines PC-3-MM2, 22Rv1, PC-3, and DU-145...
were infected with Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K (a control virus without a transgene) and analyzed with reverse transcription-PCR 24 and 48 h post-infection. Cells were analyzed with γ-spectrometer to determine the radioactive iodide content of the cells. Noninfected cells were used as a negative control. Bars, SE. *, P < 0.05; **, P < 0.01; ***, P < 0.001.

were infected with Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K (a control virus without a transgene) and analyzed with reverse transcription-PCR 24 and 48 h after infection (Fig. 2). All Ad5/3-Δ24-hNIS-infected cell lines featured a 453-bp, hNIS-specific amplification product, suggesting that hNIS is expressed from the virus genome. In contrast, Ad5/3-Δ24-Δgp19K-infected cells or cells per se did not yield an amplification product.

Ad5/3-Δ24-hNIS can mediate efficient iodide uptake into prostate cancer cells. To assess the functionality of the hNIS expressed from the virus, prostate cancer cells were infected with Ad5/3-Δ24-hNIS or Ad5/3-Δ24-Δgp19K followed by exposure to 125I and quantification of iodide accumulation (Fig. 3). When compared to noninfected or control virus-treated cells, Ad5/3-Δ24-hNIS resulted in significantly higher iodide uptake in all examined cell lines. In comparison with mock infection, Ad5/3-Δ24-hNIS caused up to 2.5 (P < 0.001) and 3 (P < 0.001) times higher iodide accumulation in PC-3MM2 and 22Rv1 cells, respectively. In PC-3 and DU-145 cells, a more modest but still significantly enhanced accumulation was seen compared with mock-treated cells [up to 1.6 (P < 0.05) and 1.3 (P < 0.001) times higher levels, respectively]. Ad5/3-Δ24-Δgp19K treatment did not result in iodide accumulation, suggesting that iodide uptake was mediated by hNIS expressed from Ad5/3-Δ24-hNIS rather than from viral infection or replication per se.

Ad5/3-Δ24-hNIS replicates in and causes oncolysis of prostate cancer cells. Prostate cancer cell lines were infected with Ad5/3-Δ24-hNIS, Ad5/3-Δ24-Δgp19K, Ad5/3-Δ24, and Ad5/3-Δ24-Δgp19K followed by exposure to 125I and quantification of iodide accumulation (Fig. 3). When compared to noninfected or control virus-treated cells, Ad5/3-Δ24-hNIS resulted in significantly higher iodide uptake in all examined cell lines. In comparison with mock infection, Ad5/3-Δ24-hNIS caused up to 2.5 (P < 0.001) and 3 (P < 0.001) times higher iodide accumulation in PC-3MM2 and 22Rv1 cells, respectively. In PC-3 and DU-145 cells, a more modest but still significantly enhanced accumulation was seen compared with mock-treated cells [up to 1.6 (P < 0.05) and 1.3 (P < 0.001) times higher levels, respectively]. Ad5/3-Δ24-Δgp19K treatment did not result in iodide accumulation, suggesting that iodide uptake was mediated by hNIS expressed from Ad5/3-Δ24-hNIS rather than from viral infection or replication per se.
The replicativity of Ad5/3-Δgp19K suggested important for retaining virus functionality (34, 35). The hNIS transgene is speed of oncolysis compared with Ad5/3-Δgp19K. In other prostate cancer cell lines, the oncolytic potency of Ad5/3-Δ24-hNIS was slightly less than Ad5/3-Δ24-Δgp19K. In fact, Ad5/3-Δ24-Δgp19K, which has the partial deletion in E3, showed the highest oncolytic potency in all examined cell lines. It is possible that the larger genome size of Ad5/3-Δ24-hNIS may affect the speed of oncolysis compared with Ad5/3-Δ24-Δgp19K. The hNIS transgene is ∼2.2 kbp, which together with the 1 kbp Δgp19K keeps the genome size <105%, which has been suggested important for retaining virus functionality (34, 35). The replicativity of Ad5/3-Δ24-hNIS was assessed in PC-3 and 22Rv1 cells where the TCID50 assay showed the increase in infectious particles in function of time (Supplementary Fig. S1).

Ad5/3-Δ24-hNIS can mediate radioactive iodide uptake into prostate cancer tumors. Subcutaneous PC-3MM2 tumors were established in NMRI/nude male mice. The bottom tumors were infected intratumorally on 2 consecutive days with 7 × 108 VP/tumor of Ad5/3-Δ24-hNIS and the top right tumor with the same dose of Ad5/3-Δ24-Δgp19K (Fig. 5A and B). The top left tumor was mock treated. A day after the last viral injection, 1.85 MBq123I/mouse was administered intravenously and mice were imaged with a γ-camera from 0.5 to 13 h after 123I injection. Some iodide accumulation into Ad5/3-Δ24-hNIS–treated tumors was seen already 0.5 h after 123I injection (data not shown). Two hours after iodide exposure, strong iodide accumulation was seen throughout Ad5/3-Δ24-hNIS–treated tumors, whereas tumors injected with control virus or saline did not uptake iodide (Fig. 5A). After 2 h, iodide accumulation reached a plateau and remained relatively constant up to the last imaging time point of the experiment 13 h after iodide injection (Fig. 5B). In addition, iodide was heavily accumulated into thyroid and stomach due to endogenous NIS expression of these organs. High stomach uptake is typically seen in mice but not in humans (36). In patients, it would be possible to protect the normal thyroid from radioiodide, but this was not done in this mouse study. Because clearance of the radioactive iodide occurs through the urine, iodide accumulation in the bladder was seen.

To quantify 123I biodistribution in vivo, organs and tumors were collected after imaging and their radioactive content was determined (Fig. 5C). Because of endogenous hNIS expression (36), the thyroid and stomach captured ∼30% of the injected dose. Nevertheless, Ad5/3-Δ24-hNIS–treated tumors accumulated >6% of the total iodide dose. This correlated with large amounts of infectious virus present in tumors, whereas only trace amounts were seen in the thyroid and stomach (Supplementary Fig. S2). Because tumors were collected >10 days after virus injection and TCID50 values measure infectious virus, high TCID50 values probably reflect virus replication. Adenoviruses lose their capsid when they enter cells; thus, input virus cannot be detected with TCID50; it requires production of new virions. Iodide uptake remained low in other organs including mock or Ad5/3-Δ24-Δgp19K–treated tumors (<1% of the initial dose).

Ad5/3-Δ24-hNIS with 131I inhibits tumor growth in vivo. To assess the efficacy of Ad5/3-Δ24-hNIS in vivo, prostate tumor-bearing mice were treated with 131I or Ad5/3-Δ24-hNIS alone or with their combination (Fig. 6). When tumors were treated with Ad5/3-Δ24-hNIS without radioiodide, tumor growth was significantly slower than in the mock or 131I alone groups (P < 0.05 for both). When mice received both Ad5/3-Δ24-hNIS and 131I, tumor sizes were significantly smaller than in any other group (all P < 0.001). Adjusted pairwise analysis indicated a significant difference between Ad5/3-Δ24-hNIS + 131I versus virus alone, 131I alone, or mock already on day 2 (all P < 0.05). The adjusted pairwise P values between Ad5/3-Δ24-hNIS + 131I versus virus alone, 131I alone, or mock on days 4, 6, and 8 were also all <0.001. Due to animal husbandry constraints, it was predefined that the experiment would be ended on day 17, although some of the mice were still in good condition. It is possible that even more benefit in the combination group might have been evident with a longer follow-up.

Whole-body emitted radioactivity was measured starting from 1 day after iodide injection. Radioactivity declined rapidly during the next 3 days as expected by clearance through kidneys (data not shown).

When tumor size reached 15 mm in any diameter, mice were killed and organs were collected for radioactivity measurements (Supplementary Fig. S3). Radioactivity declined over time and...
most radioactivity was seen in the thyroid gland and stomach and briefly in the heart probably due to propagation of $^{131}$I by circulation. In other organs, the radioactivity remained low. Importantly, virus injection did not seem to affect iodide biodistribution; therefore, the safety profile of the approach might resemble that of radioiodide therapy for thyroid cancer.

**Discussion**

Radioactive isotopes of iodine were first used for studying thyroid function and later for treatment of hyperthyroidism and other nonmalignant thyroid diseases. As hNIS is present on malignant thyroid cell membranes to variable degree (37), the use of radioiodine was extended to the treatment of thyroid cancer (38). Recently, hNIS has been used as a transgene for concentrating radioiodide to cancers of nonthyroid origin in preclinical studies (19–22, 39–43). We sought to use the established synergy between oncolytic adenoviruses and radiation (17) in the context of radioiodide given systemically but targeted to tumors by hNIS. In this approach, tumor cells are killed due to replication of the virus and by the radiation emitted by the radioiodide, and additional benefit may result from the synergy of the approaches (10, 17) and the direct bystander effect of degrading $^{131}$I $\beta$-particles that can kill untransduced neighboring tumor cells (44). Also, side effects of the treatments are nonoverlapping, which might facilitate increasing efficacy without increasing toxicity (45). Recurrent or metastatic androgen-insensitive prostate cancer requires new treatment approaches. One developmental concept is combination of radiation with oncolytic viruses (45, 46). In the context of local disease, this can be achieved with local virus injections in combination with external beam radiation or brachytherapy. Brachytherapy alone is a powerful treatment option for conformal dose delivery when the tumor size and location allow for injection of radioactive seeds. Low-energy brachytherapy ($^{125}$I or $^{103}$Pd seeds) delivers a large therapeutic dose to the prostate with little dose to other organs. However, brachytherapy is usually only practical when the tumor is restricted to the prostate. Therefore, additional approaches for targeting radiotherapy and realizing the combination of oncolytic virotherapy with radiation would be useful.

When combining direct adenovirus injection with systemic administration of $^{131}$I, there is a risk for initial radiation exposure of organs not affected by the disease. However, our data suggest that the tumor specificity of the oncolytic virus results in radiation accumulating in the tumor, whereas excretion of the iodide reduces the burden of nontarget tissue. The systemic application $^{131}$I should not be a problem because the administration of radioactive iodide is already widely used in the treatment of thyroid cancer. Moreover, our animal model showed <1% uptake of the initial dose in most organs, except for thyroid and stomach, which would be the critical organs for monitoring toxicity.

Oncolytic adenoviruses are not the only type of oncolytic viruses that have been used to express hNIS. Measles virus (47, 48) was used against ovarian cancer and myeloma in preclinical studies that preceded an ongoing phase I trial where virally expressed hNIS is used for imaging the viral propagation. Vesicular stomatitis virus has been coupled to $^{131}$I therapy with promising results (40). In contrast, oncolytic adenoviruses have not been previously used for targeting radioiodides with a therapeutic purpose. However, preclinical and clinical studies have featured hNIS armed oncolytic adenoviruses for imaging purposes (24–26). Although other viruses have their merits, oncolytic adenoviruses are appealing because they have been promising in prostate cancer (9, 11, 46) and other tumor types (7, 50, 51) in clinical trials. The safety of oncolytic adenoviruses in cancer patients has been excellent and there is also some evidence of activity, although, in general, efficacy needs improvement (8). Nevertheless, the large body of clinical data available on adenovirus in cancer treatment facilitates clinical translation of the approach described here.

We showed that oncolytic adenoviruses can effectively express hNIS as a transgene in prostate cancer cells. Also, we found that it was possible to use Ad5/3-Δ24-hNIS for concentrating sufficient amounts of radioiodide into nonthyroid cells, which has been of concern previously. Finally, viral oncolysis
together with radioiodide accumulation resulted in better anti-tumor activity in vivo than either treatment alone. Importantly, the biodistribution of radioiodide was not changed by virus infection. This suggests that the transgene was expressed selectively in tumor cells, as expected when placed under the internal adenoviral E3 promoter, which is strongly activated during virus replication. Because Ad5/3-Δ24hNIS is a tumor-selective virus, replication and subsequent hNIS expression is only expected in tumor cells (6, 28–30).

The natural existence of hNIS on most thyroid cancer cells has permitted the use of radioactive iodide for systemically administered local radiotherapy, a good example of which is oral radioiodide treatment in humans. Together with data from other groups, our results suggest that, using virus-mediated hNIS expression, the approach can be extended to treatment of cancers of nonthyroid origin. Further, our results suggest useful combination effects between radioiodide targeting and adenoviral oncolysis. However, further short-term and long-term studies are needed to evaluate the safety and efficacy of the approach. Ad5/3-Δ24hNIS may be usable in many tumor types, as its selectivity is determined by p16-Rb pathway defects, which are found ubiquitously in solid tumors. In summary, infectivity enhanced oncolytic adenoviruses armed with hNIS seem an attractive platform for improving the performance of cancers refractory to available treatments.

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

References


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