Adeno-associated virus-mediated survivin mutant Thr34Ala cooperates with oxaliplatin to inhibit tumor growth and angiogenesis in colon cancer

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Abstract. Colon cancer is one of the most common cancers. Survivin is overexpressed in human colon cancer and correlate with chemoresistance, angiogenesis and poor prognosis. Oxaliplatin, a platinum derivative cancer drug, has been used for treating human colorectal cancers. In the present study, we investigated the effect of the adeno-associated virus (AAV)-mediated survivin mutant Thr34Ala [rAAV-Sur-Mut(T34A)] on colon cancer growth. Infection with rAAV-Sur-Mut(T34A) inhibited cell proliferation, induced apoptosis and mitotic catastrophe, and sensitized colon cancer cells to chemotherapeutic drugs in vitro. Treatment with rAAV-Sur-Mut(T34A) significantly induced apoptosis, reduced angiogenesis and inhibited colon cancer growth in vivo. More importantly, rAAV-Sur-Mut(T34A) treatment strongly enhanced the antitumor activity of oxaliplatin and prolonged animal survival. Thus, the use of rAAV-Sur-Mut(T34A) in combination with chemotherapy may be a promising strategy for colon cancer therapy.
Oxaliplatin, a recently developed third-generation cisplatin analogue, has displayed clinical activity in a wide variety of tumor types. Synergistic with 5-FU in colorectal cancer (CRC), the combination has proven efficacy in 5-FU-resistant advanced disease and in previously untreated CRC. Oxaliplatin is an important new anticancer agent. In our previous study, we demonstrated that AAV-Sur-Mut(Cys84Ala) significantly enhanced the antitumor effect of 5-FU, resulted in tumor regression (22). However, the effect of AAV-mediated survivin mutant T34A alone or combination with oxaliplatin on human colon cancer growth has not been investigated. In the present study, we demonstrated for the first time that AAV-mediated-survivin-Mut(Thr34Ala) induced apoptosis, inhibited angiogenesis and tumor growth in colon cancer, and cooperated with oxaliplatin-induced tumor regression.

Materials and methods

Cell culture and chemicals. Human colon cancer cell lines HCT-116 and Colo 205 (ATCC, Rockville, MD, USA) were maintained in RPMI-1640 containing 10% fetal bovine serum (FBS), 100 U/ml penicillin, 100 μg/ml streptomycin (Gibco BRL, Life Technologies, NY, USA). Oxaliplatin (5 μg/ml) (Pharmacia and Upjohn Limited Corp., Australia) was solubilized in sterilized water and stored at 4˚C.

Construction of survivin dominant-negative mutant plasmids. We used reverse-transcribe polymerase chain reaction (RT-PCR) and an overlap extension PCR to construct pcDNA3-survivin and pcDNA3-dominant-negative mutant T34A plasmids as previously described (23). The T34A mutation was introduced by site-directed mutagenesis into pcDNA3-survivin cDNA by using the oligonucleotide 5'-GG CTGCCGCTGCgCCCCGGAGCGGTAG-3'. All of the constructs were confirmed by sequencing.

Construction and generation of recombinant AAV. We constructed 3 recombinant AAV type plasmids encoding survivin, survivin mutant (T34A) and EGFP, respectively (22). Briefly, full-length Sur(wt) and Sur-Mut(T34A) cDNAs were cut with BamHI and Xhol from pcDNA3-Survivin and pcDNA3-Sur-Mut(T34A), respectively, and subcloned into the corresponding BamHI and Xhol sites of pAM/CAG-WPRE-BGHpolyA to generate pAM/CAG-Sur-Mut(T34A). Recombinant AAV virus stocks were generated and purified by HiTrap Heparin column chromatography (Sigma Chemical Co., St. Louis, MO). The AAV viral genome titer was quantified by real-time PCR using TaqMan (Perkin-Elmer Biosystems, Foster City, CA). The viral vector was stored at -80˚C before experiments.

Flow cytometry analysis. Cells were collected and fixed in ice-cold 70% ethanol in PBS and stored at -20˚C before use. After resuspension, cells were washed and incubated with 100 μl of RNase I (1 mg/ml) and 100 μl of propidium iodide (400 μg/ml; Sigma) at 37˚C for 30 min. Samples were analyzed by flow cytometry (Coulter, Luton). The cell cycle phase distribution was calculated from the resultant DNA histogram using Multi-cycle AV software (Phoenix Flow Systems, San Diego, CA). Cells with subdiploid DNA content were considered apoptotic cells.

Western blot analysis. Cells were lysed in lysis buffer (22). Proteins were electrophoresed on 10% denaturing sodium dodecyl sulfate gel, and transferred to Immobilon-P membrane (Millipore, Bedford, MA). The blots were incubated with specific primary antibodies, reacted with a peroxidase-conjugated secondary antibody (Santa Cruz, CA) and then visualized by enhanced chemiluminescence (ECL, Amersham, Piscataway, NJ). Rabbit Survivin (71G4B7) monoclonal antibodies were purchased from Cell Signaling (Danvers, MA), Rabbit XIAP monoclonal antibody (2 μg/ml) from StressGen Biotechnologies Corp. (Victoria, BC, Canada); p-Survivin (Thr34)-R antibody, caspase 3/9, cytokeratin c and β-actin monoclonal antibodies were all from Santa Cruz Biotechnology (Santa Cruz, CA).

Immunofluorescence staining. Cells were fixed in 2% formaldehyde for 10 min and permeabilized with 0.5% Nonidet P40 in PBS. Antibodies to α-tubulin (clone DM1A) and FITC-conjugated goat anti-mouse antibodies were purchased from Sigma. Antibodies were used at 1:100 dilutions for tubulins. Nuclei were stained with 1 μg/ml Hoechst 23258 and cells were analyzed using a Zeiss Axioskop fluorescence microscope (23).

In situ detection of apoptotic cells by TUNEL assay. Apoptosis in xenograft tumors was determined by TUNEL staining (Zymed, San Francisco, CA) according to production manuals. The percentage of apoptotic cells was assessed in 10 randomly selected fields viewed at x400 magnification. The apoptotic index (A/I) was calculated as number of apoptotic cells/total number of nucleated cells x100%.

In vivo colon cancer xenograft experiment. Five to 6-week-old female BALB/c athymic nude mice were obtained from Shanghai Experimental Animals Centre of Chinese Academy of Sciences. All animal studies were conducted under approved guidelines of the Animal Care and Use Committee of Shanghai Jiaotong University. Mice were injected subcutaneously on the flanks with 1x10 6 exponentially growing HCT-116 cells. Tumors were allowed to grow to 100-150 mm3 (5-7 mm diameter). Injection was given to 3 tumor sites with rAAV-Sur-Mut(T34A), rAAV-Sur(wt) or rAAV-EGFP at 5x10 10 viral particles/site of injection or with PBS on 3 consecutive days. Alternatively, mice were intraperitoneally (IP) injected with 5 mg/kg oxaliplatin or a combination of rAAV virus and oxaliplatin for 3 days. Tumor growth was measured weekly after injection. Tumor volumes were calculated using the following formula: V (mm3) = 0.52 x length (mm) x width (mm)2 (22,23).

Immunohistochemistry staining. Coloncancer xenograft tissues were harvested after 7 days of treatment, formalin-fixed and paraffin-embedded. Tumor sections were cut in 4 μm sections and mounted on positively charged slides. All the slides were successively washed in xylene and then in decreasing concentrations of ethanol, followed by 10 min antigen retrieval in 10 mM citrate buffer (pH 6; Bio Genex, San Ramon, CA) and then incubated with CD31 (PECAM-1) monoclonal antibody (1:50; PharMingen, San Diego, CA), followed by biotinylated anti-IgG antibody (1:200; Dako) and streptavidin-biotinylated-complex/horseradish peroxidase (Dako). The sections were counterstained with hematoxylin. MVD was evaluated according to the method described...
previously (23). Areas of the highest neovascularization were chosen, and microvessel counting was performed at x200 magnification in three chosen fields. Any immunoreactive endothelial cell or endothelial cell cluster that had been distinctly separated from adjacent microvessels was considered a single countable vessel. The results regarding angiogenesis in each tumor were expressed as the absolute number of vessels/0.74 mm² (x200 field). In all assays, matched isotype control antibodies were used and found to be unreactive in all cases.

Statistical analysis. Data are expressed as means of at least 3 different experiments ± SD (standard derivations). The results were analyzed by Student’s t-test or Mann-Whitney test. P-value <0.05 was considered statistically significant. The Kaplan-Meier method was used to analyze survival of tumor-bearing mice.

Results

AAV-Sur-Mut(T34A) virus induces apoptosis in colon cancer cells. Our previous study showed that AAV can efficiently transduce colon cancer cells (22). To investigate the effect of survivin-Mut (T34A) on colon cancer growth, we generated AAV-mediated survivin mutant (T34A) virus [AAV-Sur-Mut(T34A)]. The HCT-116 colon cancer cells transduced with the AAV-Sur-Mut(T34A) and AAV-Sur(wt) virus efficiently expressed survivin protein (increased survivin expression assumed to reflect the cumulative levels of endogenous wild-type survivin and overexpressed dominant-negative mutant survivin) (Fig. 1A, upper lane). Furthermore, the expression of survivin mutant by rAAV-Sur-Mut(T34A) virus significantly down-regulated the level of endogenous Thr34-phosphorylated survivin as detected by Western blot analysis using antibody against phosphorylated Thr34 (p-Survivin 34) (Fig. 1A, middle lane) in colon cancer HCT-116 cells, confirming that rAAV-Sur-Mut(T34A) virus efficiently transduced survivin mutant (T34A) expression.

To characterize further the pro-apoptotic effect of rAAV-Sur-Mut(T34A), we analyzed apoptosis induced by transduction with rAAV-Sur-Mut(T34A), rAAV-Sur(wt) and rAAV-EGFP. Transduction of rAAV-Sur-Mut(T34A) induced apoptosis in HCT-116 and Colo 205 cell lines (Fig. 1B). Transduction of rAAV-Sur-Mut(T34A) consistently resulted in expression of mutant survivin protein and several markers of apoptosis, such as caspase 3/9 and PARP cleavage, and the release of mitochondrial cytochrome c into the cytosol (Fig. 1C). Survivin expression levels detected by immunoblotting were assumed to reflect the cumulative levels of endogenous wild-type survivin and overexpressed dominant-negative mutant survivin (Fig. 1C). In contrast, there was no significant change in expression of other IAP genes (XIAP, cIAP1, cIAP2) in cells transfected with rAAV-Sur-Mut(T34A) (data not shown).

AAV-Sur-Mut(T34A) induces mitotic catastrophe in colon cancer cells. Ours and other studies have indicated that the inhibition of survivin function caused mitotic catastrophe (23). We examined whether transduction of AAV-Sur-Mut(T34A) could induce mitotic catastrophe in colon cancer cells. We found that infection of AAV-Sur-Mut(T34A) increased the number of cells with multiple nuclei in HCT-116 cells (Fig. 2A). Consistent with these observations, cells that were transduced with AAV-Sur-Mut(T34A) showed a significant increase in abnormal nuclei, including micronucleated, multilobulated and abnormally large nuclei 72 h after transduction, relative to cells transduced with rAAV-Sur(wt) and rAAV-EGFP (Fig. 2B). Our results show that the AAV-mediated survivin mutant (T34A) causes mitotic catastrophe in colon cancer cells.

AAV-Sur-Mut(T34A) virus sensitizes colon cancer cells to oxaliplatin-induced apoptosis. 5-Fluorouracil (5-FU) is the first-choice chemotherapy drug for colorectal cancer. Oxaliplatin is used for the treatment of advanced colorectal
cancer that is resistant to 5-FU (24). Ectopic expression of survivin increased the resistance of colon cancer to oxaliplatin. Thus, we asked whether ectopic expression of survivin-Mut(T34A) could sensitize colon cancer to apoptosis induced by oxaliplatin. We examined the pro-apoptotic effect of rAAV-Sur-Mut(T34A) combined with the agents on cancer cells. The results showed that the rate of apoptosis was increased >2.5-fold when a combination of oxaliplatin and rAAV-Sur-Mut(T34A) virus was used relative to either treatment group alone (Fig. 3). In contrast, transduction with rAAV-Sur(wt) counteracted apoptosis induced oxaliplatin. These results demonstrate that rAAV-Sur-Mut(T34A) sensitizes colon cancer cells to chemotherapeutic drugs.

rAAV-Sur-Mut(T34A) inhibits tumor growth in vivo. We examined the effect of rAAV-Sur-Mut(T34A) on subcutaneous

Figure 2. rAAV-Sur-Mut(T34A) Virus transduction induces mitotic catastrophe in colon cancer cells. (A) HCT-116 cells transduced with rAAV-Sur(wt), rAAV-EGFP or rAAV-Sur-Mut(T34A) for 72 h were stained for microtubules with an anti-r-tubulin antibody. Arrow shows abnormal large and multilobed nuclei. Photomicrographs are from representative experiments performed in triplicate. Original magnification, x400. (B) Quantification of mitotic catastrophe. Approximately 500-600 nuclei were scored on 5 random 400 x objective fields in triplicate as described. The experiment was performed independently, and the results presented are the means ± SD obtained from 3 independent experiments. *P<0.01 compared with group transduced with rAAV-Sur(wt) and rAAV-EGFP.

Figure 3. rAAV-Sur-Mut(T34A) virus sensitizes colon cancer cells to oxaliplatin-induced apoptosis. HCT-116 cells were infected with rAAV at 1×10^7 viral particle/cell followed by 1 μg/ml of oxaliplatin for an additional 72 h. Apoptosis was determined by FACS analysis. The results represent the mean ± SD of 3 independent experiments. *P<0.05, compared to oxaliplatin treatment alone; #P<0.05, compared to other treatment groups, respectively.
colon cancer xenograft tumors. The HCT-116 cells were injected into the flank of athymic female nude mice. Tumors with 100-150 mm³ volume were injected in 3 sites with indicated rAAV virus at 5x10¹⁰ viral particles/site of injection or with PBS. Tumor growth was measured every week after injection. Data are the means ± SD of tumor size per mouse. (B) AAV-mediated survivin mutant (T34A) expression induces apoptosis and inhibits tumor angiogenesis in vivo. Tumor sections from TUNEL staining for detection of apoptotic cells or immuno-histochemical stained for CD31 (angiogenesis) (original magnification, x200). *P<0.05. Arrows show apoptotic cells (upper lane) and CD31-positive cells (lower lane), respectively. (C) Quantification of apoptosis of tumor cells. TUNEL staining was shown (B). The number of apoptotic cells was assessed in 10 randomly selected fields of each slide viewed at x40 magnification. Data are the mean ± SD of the apoptotic index from 9 sections of 3 animals per group. (D) Quantification of blood microvessel density (BMD). CD31 staining is shown (B). Areas of highest vascularization were chosen at low magnification, x100). Microvessel counting was performed at x200 on three chosen fields. Results are the mean of independent determinations by two investigators. Data represent the mean ± SD (n=5).

Figure 4. rAAV-Sur-Mut(T34A) inhibits tumor growth in vivo. (A) The HCT-116 cells were subcutaneously injected into the right flank of athymic female nude mice. Tumors with 100-150 mm³ volume were injected in 3 sites with indicated rAAV virus at 5x10¹⁰ viral particles/site of injection or with PBS. Tumor growth was measured every week after injection. Data are the means ± SD of tumor size per mouse. (B) AAV-mediated survivin mutant (T34A) expression induces apoptosis and inhibits tumor angiogenesis in vivo. Tumor sections from TUNEL staining for detection of apoptotic cells or immuno-histochemical stained for CD31 (angiogenesis) (original magnification, x200). *P<0.05. Arrows show apoptotic cells (upper lane) and CD31-positive cells (lower lane), respectively. (C) Quantification of apoptosis of tumor cells. TUNEL staining was shown (B). The number of apoptotic cells was assessed in 10 randomly selected fields of each slide viewed at x40 magnification. Data are the mean ± SD of the apoptotic index from 9 sections of 3 animals per group. (D) Quantification of blood microvessel density (BMD). CD31 staining is shown (B). Areas of highest vascularization were chosen at low magnification, x100). Microvessel counting was performed at x200 on three chosen fields. Results are the mean of independent determinations by two investigators. Data represent the mean ± SD (n=5).

HT-29 cells xenograft. Single intratumor administration of rAAV-Sur-Mut(T34A), rAAV-EGFP, inhibited HT-29 xenograft growth by ~58.7 and 33.4% at 5 weeks, compared with groups injected with PBS. These results showed that single intratumor administration of rAAV-Sur(wt) significantly inhibited colon cancer growth.

rAAV-Sur-Mut(T34A) induces apoptosis and inhibits tumor angiogenesis in vivo. We further investigated the in vivo mechanism by which rAAV-Sur-Mut(T34A) inhibits tumor
growth. Tumors injected with rAAV-Sur-Mut(A34T) virus expressed high levels of survivin mutant protein (data not shown) 42 days after injection of rAAV virus. Consistent with the expression of survivin mutant protein, TUNEL-positive cells (apoptotic cells) were significantly higher in the tumors injected with rAAV-Sur-Mut(T34A) virus compared to other tumors injected with PBS, rAAV-EGFP and rAAV-Sur(wt) (Fig. 4B). These results indicated that rAAV-Sur-Mut(T34A) virus may mediate long-term expression of survivin mutant and induce apoptosis in colon cancer in vivo.

It has been reported that survivin could promote capillary formation in vitro (25,26). We examined whether over-expression of survivin mutant protein (T34A) could inhibit tumor angiogenesis in colon cancer. Immunohistochemical staining of endothelial cell-derived CD31 in colon cancer xenografts showed that the tumors injected with rAAV-Sur(wt) and AAV-GFP exhibited an extensive network of viable blood vessels, consistent with tumor-associated angiogenesis. In contrast, intratumor injection of rAAV-Sur-Mut(T34A) resulted in a significant reduction in the number of viable blood vessels by CD31 staining (Fig. 4B). Quantification analysis of CD31-stained areas showed injection of AAV-Sur-Mut(T34A) in tumor resulted in significant suppression of blood vessel density in colon cancer xenografts, when compared with Ad-AAV-Sur(wt), AAV-EGFP and PBS (Fig. 4C).

rAAV-Sur-Mut(T34A) enhances the effect of antitumor chemotherapeutic drugs in vivo. We further investigated the combination effect of rAAV-Sur-Mut(T34A) and oxaliplatin on tumor growth. These tumors were injected in 3 sites with rAAV-Sur(wt), rAAV-EGFP or rAAV-Sur-Mut in 3 sites (5x10^10 particles virus/site) in combinations of oxaliplatin injection (5 mg/kg). The experiments were repeated twice. Tumor growth was measured every week after injection. Data are the means ± SD of tumor size per mouse 5 weeks after treatment. *P<0.05, compared to PBS group; **P<0.05, compared to rAAV-EGFP group; ***P<0.05, compared to other treatment groups. (B) The combination of rAAV-Sur-Mut(T34A) and oxaliplatin prolongs animal survival. The experimental conditions were the same as in (A). Survival was monitored every day, and tumor volume was measured every week after treatment. Definition of death is natural death because of tumor burden or sacrificed because of tumor sizes (diameter) >2.5 cm (n=10).

Figure 5. The combination of rAAV-Sur-Mut(T34A) oxaliplatin to enhances antitumor in vivo. (A) The combination of rAAV-Sur-Mut(T34-A) and oxaliplatin synergistically inhibits tumor growth. Tumors ~100-150 mm^3 volume was injected with PBS, rAAV-EGFP, or rAAV-Sur(wt) or rAAV-Sur-Mut in 3 sites (5x10^10 particles virus/site) in combinations of oxaliplatin injection (5 mg/kg). The experiments were repeated twice. Tumor growth was measured every week after injection. Data are the means ± SD of tumor size per mouse 5 weeks after treatment. *P<0.05, compared to PBS group; **P<0.05, compared to rAAV-EGFP group; ***P<0.05, compared to other treatment groups. (B) The combination of rAAV-Sur-Mut(T34A) and oxaliplatin prolongs animal survival. The experimental conditions were the same as in (A). Survival was monitored every day, and tumor volume was measured every week after treatment. Definition of death is natural death because of tumor burden or sacrificed because of tumor sizes (diameter) >2.5 cm (n=10).
survived significantly longer than PBS-treated mice (P<0.05), all eventually died (Fig. 5B). Notably, 5 out of 8 animals treated with the combination of rAAV-Sur-Mut(T34A) and oxaliplatin were still alive without any visible tumors and without clinical symptoms 100 days after treatment. Furthermore, all the animals survived significantly longer than mice treated with rAAV-Sur-Mut(T34A) or oxaliplatin (P<0.01) (Fig. 5B).

Discussion

Survivin expression is associated with the inhibition of apoptosis and poor progression in cancer patients. Thus, targeting survivin pathway for cancer therapy has been widely investigated (18,25,27-29). The studies have shown that the mutagenesis of Thr34-Ala completely suppressed survivin phosphorylation by p34cyc1-cyclin B1 in vitro and in vivo (17,30). The inducible expression (28) or adenosial delivery (18) of non-phosphorylatable survivin mutant (T34A) prevented phosphorylation of endogenous survivin, induced apoptosis and inhibited tumor growth in human breast and prostate cancer and mouse colon cancer in vivo (18,19,28,31,32). In this study, we demonstrated that AAV-mediated survivin-Mut (T34A) induced apoptosis of human colon cancer in vitro and in vivo, reduced angiogenesis and inhibited colon cancer growth in vivo. The treatment of rAAV-Sur-Mut(T34A) virus strongly enhanced the antitumor activity of oxaliplatin and prolonged animal survival.

Tumor angiogenesis plays an important role in tumor development and progression. Several studies have shown that the elevated survivin expression is associated with increased microvessel density in colorectal cancer (9), colon cancer (23) and brain glioma (33). Increased survivin expression has been verified in endothelial cells during the proliferative (25,34,35) and remodeling (36,37) phases of angiogenesis, potentially serving as a cytoprotective mechanism for these cells (35). Importantly, induction of survivin in endothelial cells is associated with resistance to apoptosis. In contrast, survivin is undetectable in quiescent endotelium in vitro and in vivo (25), and targeting survivin does not affect endothelial cell viability in quiescent endothelium (33). Thus, inhibition of survivin may promote endothelial cell apoptosis during tumor angiogenesis, accelerating regression of newly formed blood vessels and reducing the incidence of metastatic disease. In this study, we found that rAAV-mediated Sur-Mut(T34A) could markedly suppress tumor angiogenesis in vivo. This was consistent with our previous results that rAAV-mediated Sur-mut(Cys84Ala) induced endothelial cell apoptosis and reduced angiogenesis in colon cancer (22). Our data showed that the selected expression of survivin dominant mutant in tumor cells may provide a high degree of specificity for potential survivin antagonists to enhance both anti-angiogenic and anti-neoplastic therapeutic strategies.

Chemotherapy is still one of major strategies for advanced colon cancer therapy. However, drugs resistance is still a potential clinical problem. It has been demonstrated that overexpression of survivin contributes to drug-resistance (37,38) and that anticancer drugs inducing G2-M arrest with elevated or residual p34/35 kinase activity caused Thr34 phosphorylation and increased survivin levels (27). 5-FU and oxaliplatin have been shown to induce G2/M arrest in a variety of cell lines and induce apoptosis (39-41). In this study, overexpression of survivin mediated by rAAV virus reduced oxaliplatin-induced cells apoptosis, consistent with previous reports that the ectopic expression of survivin contributes to tumor-resistance of drugs (27,42). Accordingly, the expression of Sur-Mut(T34A) mediated by AAV sensitized colon cancer cells to oxaliplatin (42). Furthermore, the combination of oxaliplatin and rAAV-mediated Sur-Mut(T34A) significantly inhibited tumor growth in vivo than rAAV-Sur-Mut(T34A) only injection and oxaliplatin only treatment. Our study demonstrated a synergistic effect of the combination of targeting survivin gene therapy and chemotherapy. Use of oxaliplatin as second-line therapy for advanced colorectal cancer has shown some promise in cases where 5-fluouracil has failed. Thus, the findings described here may have practical implications for potential strategies for colon cancer therapy.

In summary, our study documented the therapeutic potential of rAAV mediated Sur-Mut(T34A) in the treatment of colon cancer, especially in combination with chemotherapeutic intervention. Our results showed that targeting the survivin pathway is a novel anti-angiogenic and anti-neoplastic therapeutic strategy.

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References


