

Anti-tumor effects of engineered mesenchymal stem cells in colon cancer model

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Background: Cell-based gene therapy is considered as a promising strategy for the treatment of human malignancy. In many different types of cancer, mesenchymal stem cells (MSCs) are observed as valuable and potential anti-cancer agents. However, the exact mechanisms of MSCs involved in tumor microenvironment are not well understood.

Aim: Our aims are to elucidate the MSCs-mediated tumor microenvironment.

Materials and methods: In this study, colon cancer model was established by injecting the HT29 cells into the subcutaneous of right axilla of nude mice. We applied the human placenta-derived MSCs (hP-MSCs) armed with a double fusion gene containing the herpes simplex virus truncated thymidine kinase and firefly luciferase for treatment of colon cancer on days 10, 15, and 20 after HT29 cells injection. Molecular imaging methods were used for real-time imaging tumor progression and tracking transplanted hP-MSCs by bioluminescence imaging. Furthermore, proliferation and apoptosis-related proteins levels in colon cancer tissues were examined by immunofluorescence and Western blotting.

Results: Our results demonstrated that the administration of engineered hP-MSCs significantly inhibited the tumors and this effect was enhanced by ganciclovir application. Further analysis demonstrated the anti-tumor effect of engineered hP-MSCs in vivo depended on inhibiting tumor proliferation and inducing tumor apoptosis.

Conclusion: Collectively, this work showed that engineered hP-MSCs could inhibit colon cancer progression and metastasis by inducing tumor cell death and suppressing proliferation.

Keywords: tumor microenvironment, mesenchymal stem cells, malignant tumor, gene therapy, bioluminescence imaging

Introduction

Colon cancer is a common malignant tumor, and its morbidity and mortality are on the rise in recent years.¹ It is a serious threat to people's health and life.² Traditional radiotherapy, chemotherapy and surgical treatment can kill tumor cells but also cause great damage to normal cells.³ Therefore, it is urgent to find a new therapeutic method that can target tumor cells without harming normal cells. Mesenchymal stem cells (MSCs) are a kind of pluripotent stem cells with multidirectional differentiation potential derived from mesoderm and mainly exist in connective tissue and interstitium of organs.⁴⁻⁶ Under suitable conditions, MSCs can be induced to differentiate into adipose tissue, bone, cartilage and other tissue cells.⁷ MSCs have low immunogenicity, immunomodulatory ability, the ability to be easily cultured and amplified in vitro and migrate to tumor or inflammatory sites, so they have been widely used in the experimental and clinical studies of inflammation and tumor diseases.⁸⁻¹⁰

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Recently, MSCs have been used as a cell carrier to participate in tumor-targeted therapy,^{11,12} and studies have shown that gene-modified MSCs could continuously and stably produce therapeutic factors to play a role in tumor inhibition after reaching tumor sites, providing a new possibility for tumor immunotherapy.^{13–15} Tumor growth and development require support from the surrounding stroma. A large number of studies have shown that tumor cells could locally produce high concentrations of cytokines in tumor microenvironment, which was conducive to the migration of MSCs to tumor tissue and participate in the construction of tumor microenvironment.^{16,17} These cytokines mainly include: vascular endothelial growth factor, fibroblast growth factor, platelet-derived growth factor, hepatocyte growth factor, monocyte chemoattractant protein-1 (MCP-1) and epidermal growth factor.¹⁸ The research showed that MCP-1 was expressed in all breast cancer cells, and it was confirmed that MCP-1 played an important role in the migration of MSCs to breast cancer.^{19,20}

Some studies have shown that MSCs could deliver several oncolytic viruses, antiangiogenic factors, and substrates expressing prodrug enzyme conjugates to produce toxic effects.²¹ MSCs expressing simplex virus thymidine kinase showed strong anti-tumor effects in pancreatic cancer mouse model after intraperitoneal injection of substrates ganciclovir (GCV).²² Moreover, the application of MSCs carrying HGF and NK4 antagonists to the lung metastasis model of colon cancer showed a significant increase in survival time,²³ which was consistent with the induction of apoptosis of tumor cells by inhibiting tumor-related angiogenesis.^{22,24}

In this study, we explored, by *in vitro* and *in vivo* investigations, the feasibility and efficacy of engineered MSCs-double fusion (DF) as cellular vehicles of the therapeutic gene herpes simplex virus truncated thymidine kinase (HSV-ttk) in the treatment of human colon cancer (HT29). We hypothesized that *in vivo* imaging technology could better guide the presentation of MSCs and monitor the behavior of MSCs *in vivo* in real time. Based on this hypothesis, MSCs derived from human placenta were used as cell vectors to mediate the treatment of colon cancer in animal models. We used the dual reporter genes renilla luciferase (Rluc) and firefly luciferase (Fluc) in the same animal to detect tumor development and mesenchymal cell survival, respectively.

Materials and methods

Cell culture

The HT29 cell line from ATCC (Manassas, VA, USA) was maintained at 37°C in a humidified 5% CO₂ incubator and cultured in DMEM/F12 medium (Gibco, Grand Island, NY, USA) supplemented with 10% FBS (HyClone, Logan, UT, USA) and 1% penicillin/streptomycin (Gibco). Human placenta (hP)-MSCs were isolated as in previously described protocols²⁵ and cultured in DMEM/F12 medium (Gibco) with 10% FBS (HyClone) and 1% penicillin/streptomycin (Gibco).

Lentivirus transduction

Fluc-HSV-ttk and Rluc-green fluorescence protein (GFP) reporter plasmids were obtained from Addgene. 293T cells were transfected with Fluc-HSV-ttk or Rluc-eGFP reporter and packaging vectors psPAX2 and Pmd2.G to produce virus for stable cell line generation. The viruses were collected by removing the cell media at 48 hrs after transfection. Infection was performed with 1 mL of lentivirus supplemented with 5 µg/mL polybrene (Sigma, St Louis, MO, USA) in six-well plates for 2 days. hP-MSCs were transduced with the lentiviral vector carrying an ubiquitin promoter driving Fluc and HSV-ttk reporter gene. The system of herpes simplex virus thymidine kinase-glycoguanine system (HSV1-TK/GCV) has been the most widely used in cancer suicide gene therapy. Moreover, HT29 cells were labeled with the lentiviral vector carrying an ubiquitin promoter driving Rluc and enhanced GFP (eGFP) DF reporter gene.

Establishment of tumor model

Male Nu/Nu nude mice (8–10 weeks old) were obtained from Laboratory Animal Center of the Academy of Military Medical Science (Beijing, China) and kept in an SPF (Specific Pathogen Free) environment. All experimental procedures were approved by the Animal Care and Use Committee of Anhui No. 2 Province People's Hospital, Hefei, China, and were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. HT29 cells (HT29-DF) transfected with DF gene (Flu-eGFP) were prepared into a 200 µL single-cell suspension (the cell concentration was 5×10⁶/mL) with PBS and injected into the subcutaneous of right axilla of nude mice. The drinking water and feed of mice were treated with sterility, and the feeding environment was laminar flow. Tumor formation was observed 10 days

after transplantation, and the mice were divided into 1) PBS group (the tail vein was injected with 200 μ L PBS), 2) the MSCs-DF group (200 μ L MSCs-DF were injected into the tail vein), and 3) the MSCs-DF+GCV group (200 μ L MSCs-DF+GCV were injected into the tail vein).

Bioluminescence imaging

Fluc and Rluc with different cell numbers of activity and the fate of transplanted cells were confirmed by bioluminescence imaging (BLI) (IVIS Lumina II System; Xenogen Corporation, Hopkinton, MA, USA). For BLI in vivo, each mouse was imaged for 1–3 mins using the IVIS Lumina Imaging System at different time point. D-Luciferin (150 mg/kg) and coelenterazine (2.5 mg/kg) were intraperitoneally injected into mice for evaluating Fluc and Rluc expression, respectively. The signal intensity was analyzed by utilizing the software of living image. Average radiance of peak BLI signal was quantified by from a fixed-area region of interest over abdomen.

Immunofluorescence staining assay

At day 28 after transplantation of HT29-DF cells, the mice were euthanized and tumor samples were harvested and fixed. Immunofluorescence staining assay was performed to detect the proliferation protein of tumor cells by using Ki-67 Monoclonal Antibody (Invitrogen, Carlsbad, CA, USA). In addition, the apoptosis of tumor cells was detected by the Apoptosis Assay Kit (Beyotime, Shanghai, China). 594 goat anti-rabbit IgG (Invitrogen) was applied appropriately. The cell nuclei were counterstained with DAPI. The images were analyzed by Image J software (National Institutes of Health, Bethesda, MD, USA).

Western blotting

For protein analysis, all tumor sample extracts of tumor (50–100 mg) were lysed with (radio-immunoprecipitation assay) RIPA lysis buffer (Coweil, Beijing, China) containing proteinase inhibitors on ice for at least 0.5 hrs. BCA Protein Assay Kit (Promega, Madison, WI, USA) was used to quantify the concentration of proteins. Three independent replicates of 30 μ g sample were applied to detect the protein expression level with a primary antibody. The primary antibodies used include PCNA (1:1000, Abcam, Cambridge, UK), Caspase-3 (1:2000, Cell Signaling Technology, Boston, MD, USA), and GAPDH (1:1000, Abcam).

Statistical analysis

All experiments were repeated at least three times and data are expressed as mean \pm standard error of measurement (SEM). An independent Student's *t*-test was used for two-group comparisons, and one-way ANOVA for multiple-group comparison. For statistical analysis, GraphPad Prism software version 5.0 (GraphPad Software, Inc., La Jolla, CA, USA) was performed to analyze the quantitative data. $P < 0.05$ was defined as significant difference.

Detailed methods for the determination of vector incorporation rate can be found in the [Supplementary materials](#).

Results

Characterization of transplanted cells

The transgene of interest containing the Fluc and HSV-ttk DF reporter gene was introduced into early passage hP-MSCs (Figure 1A). The phenotype of MSCs and MSCs-DF was presented in Figure S1 and the vector incorporation rate was determined in MSCs-DF (Figure S2). The activity of Fluc was detected by BLI to demonstrate the ability of tracking the cell fate in vivo. BLI results showed a good correlation between cell numbers and firefly signal intensity in MSCs-DF cells (Figure 1B and C). Moreover, in order to track the tumor cells, we transduced HT29 cells with DF reporter gene consisting of Rluc and eGFP (Figure 1D). And likewise, the correlation between cell number and Rluc activity of HT29-DF was detected by BLI. The results suggested that the renilla signal intensity could be used to assess the tumor growth in vivo (Figure 1E and F).

MSCs-DF/GCV mediated cytotoxicity and bystander effect for HT29 cells in vitro

To detect the efficiency of the HSV-ttk suicide gene system, we treated MSCs-DF with different concentrations of GCV (0, 5, 10, 20, 30 and 40 μ g/mL). When the fusion degree of MSCs-DF reached 80%, we started to give GCV. The number of MSCs-DF cells could be detected by BLI technology at 24, 48 and 72 hrs, respectively (Figure 2A). We found that the number of cells were significantly decreased with increasing GCV concentration, and when the concentration of GCV reached 40 μ g/mL, more than 70% of the cells had died after 72 hrs of GCV treatment (Figure 2B). At the same time, we also analyzed the effect of suicide gene efficiency over time. We tested the number of MSCs-DF cells for three consecutive days after GCV administration by BLI. We found that the number of

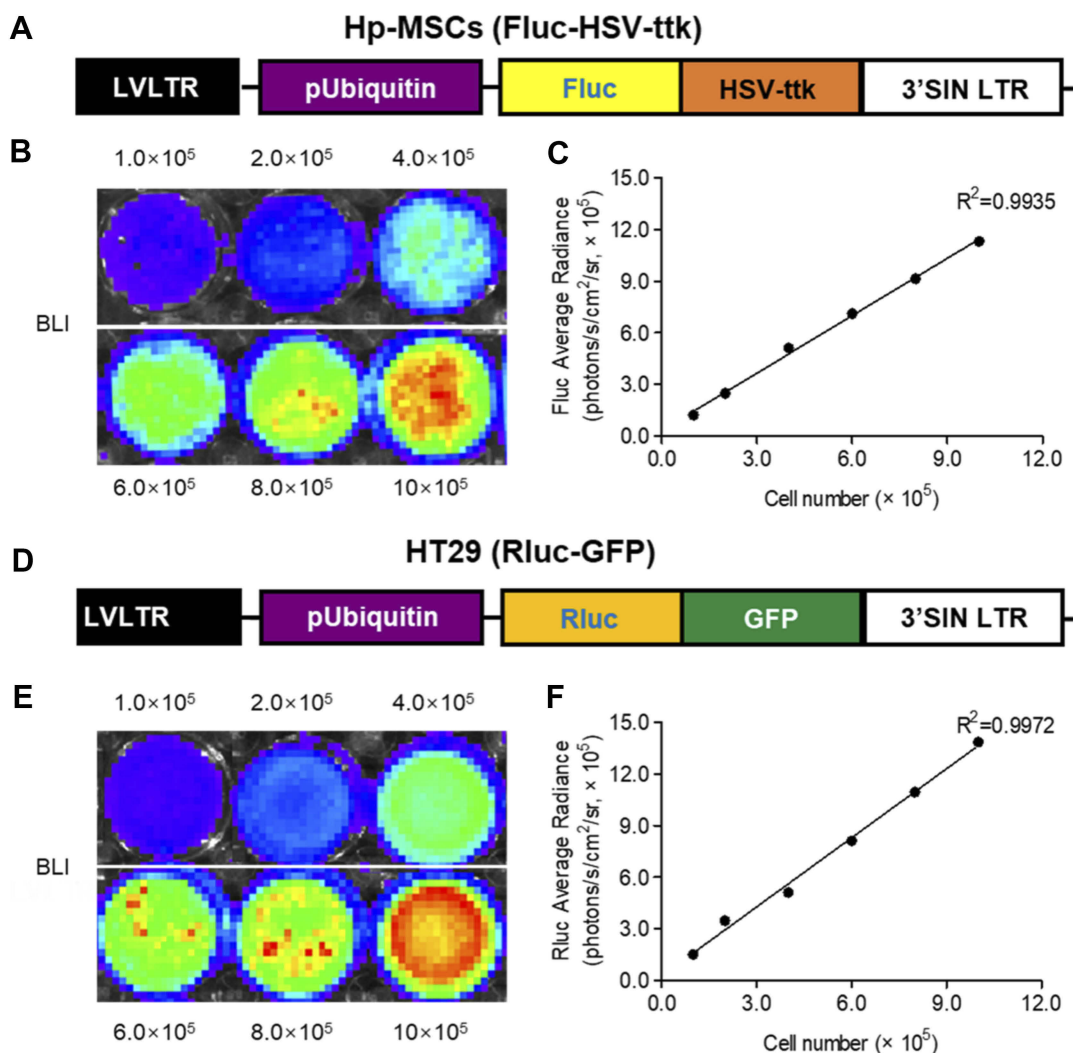


Figure 1 Transduction of hP-MSCs and HT29 cells with DF reporter genes, respectively. **(A)** The DF reporter gene composed of Fluc and HSV-ttk was driven by an ubiquitin promoter. **(B and C)** Imaging signals analysis of stably transduced hP-MSCs shows a good correlation between cell numbers and Fluc reporter gene activity in vitro. **(D)** The DF reporter gene composed of Rluc and eGFP was driven by the ubiquitin promoter. **(E and F)** The analysis of the image data showed that there was a strong correlation between the cell numbers of HT29 cells and the activity of the Fluc reporter gene, which were stably transfected. **Abbreviations:** hP-MSCs, human placenta-derived MSCs; DF, double fusion; Fluc, firefly luciferase; HSV-ttk, herpes simplex virus truncated thymidine kinase; Rluc, renilla luciferase; GFP, green fluorescence protein; BLI, bioluminescence imaging; MSC, mesenchymal stem cells.

MSCs-DF cells expressing suicide genes continued to decline over time.

Next, we evaluated the bystander effect of the suicide gene system on colon cancer cells. We mixed different proportions of MSCs-DF cells with HT29-DF cells in different quantitative gradients and treated with 40 µg/mL GCV. Changes of HT29-DF cells viability in each proportional group were measured after 1, 2 and 3 days, respectively. Since Rluc is expressed in HT29-DF cells, the cell viability can be reflected by analyzing the detection of Rluc signal in HT29-DF cells (Figure 2C). Statistical analysis of the results of imaging revealed that as the proportion of MSCs-DF/HT29-DF cells increased,

the viability of HT29-DF cells decreased accordingly. When the ratio of the number of cells reached 1:1, the cell viability of HT29-DF was <20% of the cell viability of the control group (Figure 2D). Meanwhile, we further analyzed the effect of suicide gene on the bystander effect of HT29-DF cells over time. The results showed that the proliferation of HT29-DF cells was inhibited as the GCV treatment time increased compared with the control (treated with PBS) group (Figure 2E).

Effects of MSCs-DF on tumor growth

To evaluate the effects of transplanted MSCs-DF on the growth of colon cancer, we introduced Fluc imaging to

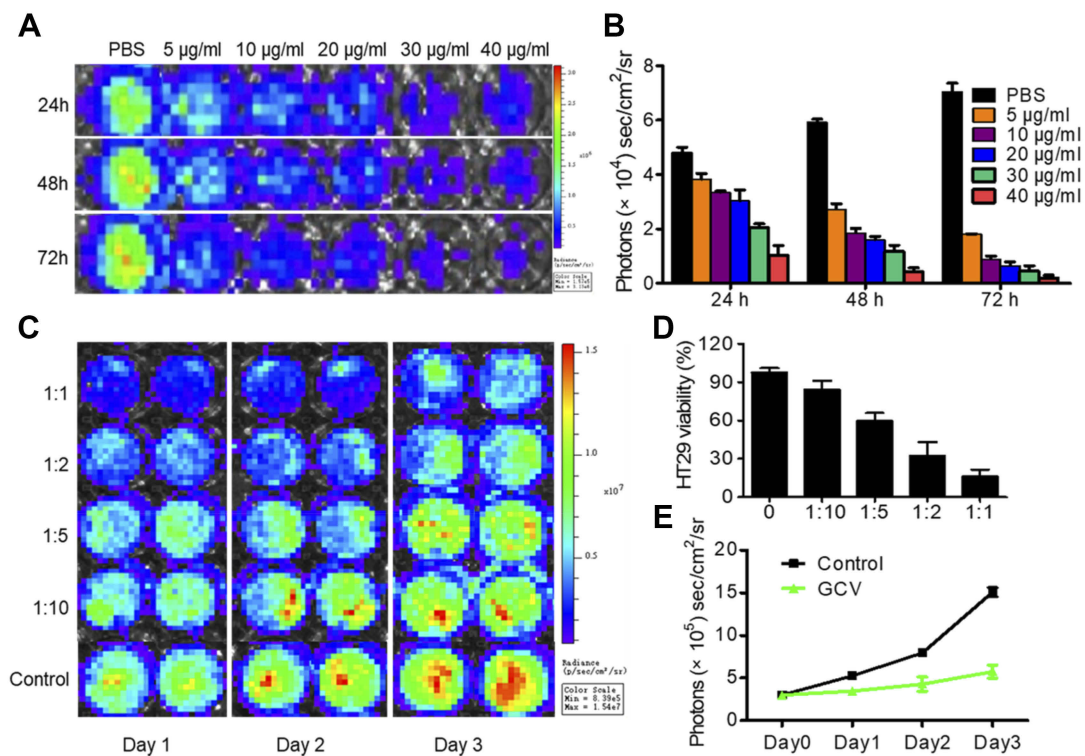


Figure 2 MSCs-DF were highly sensitive to GCV and had the bystander effect on HT29 cells in vitro. (A) MSCs-DF cells were plated and treated with different concentrations of GCV (0, 5, 10, 20, 30 and 40 µg/mL). The survival of MSCs-DF cells was determined by BLI assay for 3 days. (B) BLI signals were quantitatively analyzed in the presence of different concentrations of GCV, and the signal activity was expressed as photons/s per cm² per steradian (sr). (C) Mixtures of MSCs-DF and HT29-DF cells in the ratios (MSCs-DF:HT29-DF = 0, 1:10, 1:5, 1:2, 1:1) were plated and were treated with GCV (40 µg/mL), and the numbers of HT29-DF cells were revealed by BLI assay for 3 days. (D) The viability of HT29 cells was measured by the relative radiance compared to Control on day 3. (E) When the ratio of MSCs-DF cells to HT29 cells was 1:1, the cell viability of HT29 was measured as mentioned above. Experiments were performed in triplicate. MSCs-DF, hP-MSCs-DF; MSCs-DF+GCV, hP-MSCs-DF+GCV. **Abbreviations:** hP-MSCs, human placenta-derived MSCs; MSC, mesenchymal stem cells; DF, double fusion; BLI, bioluminescence imaging; GCV, ganciclovir.

monitor tumor progression. The outline of MSCs-DF in the treatment of tumor is shown (Figure 3B). 1×10^6 HT29-DF cells were injected into the subcutaneous of right axilla of Nu/Nu nude mice to establish a colon cancer model. After 10 days, 1×10^6 MSCs-DF were injected into mouse by the tail vein at 10, 15 and 20 days, respectively. GCV (30 mg/kg) or PBS were intraperitoneally injected into mice at days 11–13, 16–18, 21–23 after the injection of MSCs-DF. Rluc activity was detected by BLI to track tumor development. The results showed that tumor growth was inhibited to a certain extent after transplantation of MSCs-DF, while the use of GCV promoted tumor inhibition (Figure 3A and C). These findings are consistent with previous reports.¹⁰ In addition, the detection of Fluc signal was used to evaluate the fate of transplanted MSCs-DF in vivo. Imaging signals showed that the transplanted MSCs-DF could migrate to the tumor site, and its survival was gradually reducing with the passage of time. The use of GCV could significantly reduce the survival of MSCs-DF (Figure 3D and E).

Effects of MSCs-DF on tumor proliferation and apoptosis

To further demonstrate the inhibition effect of MSCs on tumor growth, we performed immunofluorescence staining on tissues on day 28. The staining of the proliferating protein Ki67 showed that the transplanted MSCs-DF could inhibit the proliferation of the tumor, and this effect was enhanced in the MSCs-DF+GCV group (Figure 4A). Statistical analysis of TUNEL staining results showed that the positive rate of TUNEL staining in the mice transplanted with MSCs-DF+GCV was significantly higher than that of the other groups (Figure 4B). These results suggested that the inhibitory effect of transplanted MSCs-DF on tumors was achieved not only by affecting tumors proliferation but also by promoting tumor apoptosis. In addition, we used Western blot to detect the expression of PCNA and Caspase-3. The results showed that the cell proliferation protein PCNA was slightly decreased in the MSCs-DF group compared with the control group, while the expression was significantly reduced in MSCs-DF+GCV

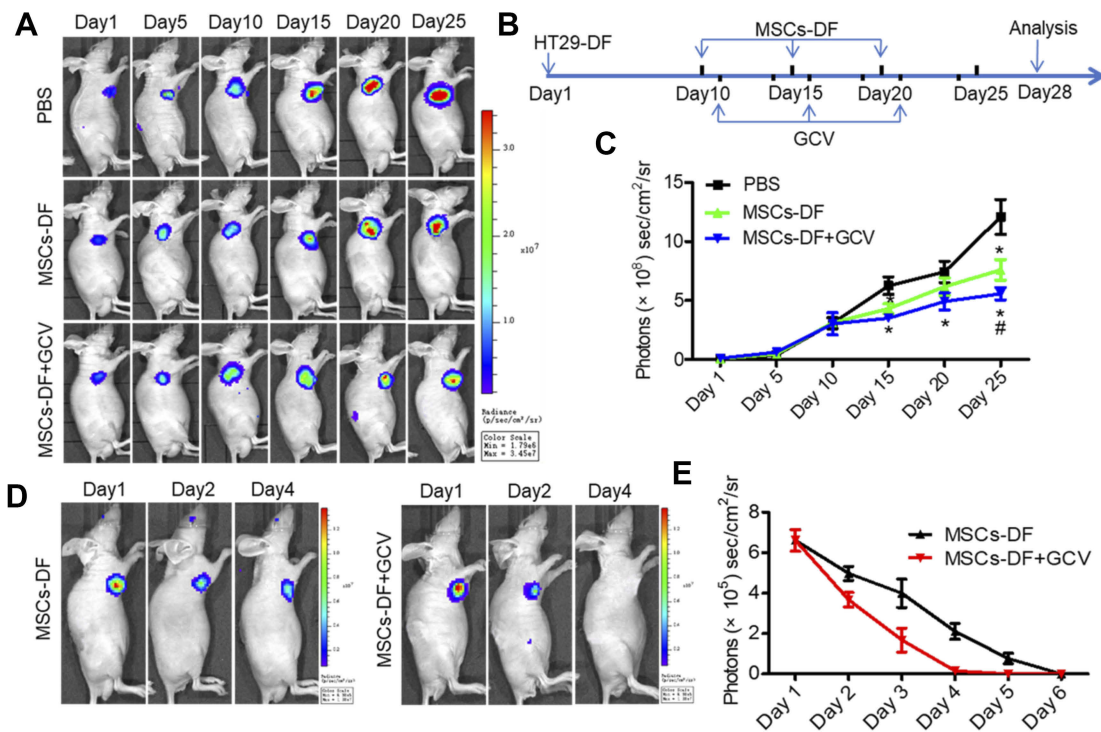


Figure 3 MSCs-DF inhibited tumor growth through the HSV-ttk system in vivo. **(A)** Rluc imaging of tumor progression. **(B)** Schematic diagram of MSCs-DF cells in the treatment of colon cancer. **(C)** Quantitative analysis of Rluc signal. Data are expressed as mean \pm SEM, n=6. *P<0.05 versus PBS; #P<0.05 versus MSCs-DF. **(D)** Fluc imaging of MSCs-DF with GCV and without GCV. **(E)** BLI signals were quantitatively analyzed, and the signal activity was expressed as photons/s/cm²/steradian (sr). Experiments were performed in triplicate. MSCs-DF, hP-MSCs-DF; MSCs-DF+GCV, hP-MSCs-DF+GCV. **Abbreviations:** MSC, mesenchymal stem cells; DF, double fusion; HSV-ttk, herpes simplex virus truncated thymidine kinase; Rluc, renilla luciferase; Fluc, firefly luciferase; GCV, ganciclovir; BLI, bioluminescence imaging; hP-MSCs, human placenta-derived MSCs.

group. In contrast, the MSCs-DF group was able to up-regulate the expression of the apoptotic protein Caspase-3, which was further enhanced in the MSCs-DF+GCV group (Figure 4C and D). The results were consistent with the results of immunofluorescence staining. This further illustrated the effect of MSCs on the proliferation of colon cancer cells, mainly through the bystander effect.

Discussion

In this study, we investigated the relationship between engineered hP-MSCs and tumor formation by using the bioluminescence in vivo imaging system for visual detection. The results showed that systemic transplantation of engineered MSCs could inhibit tumor growth by inducing apoptosis of tumor cells. Meanwhile, MSCs carrying suicide genes (HSV-ttk) could further kill tumors through bystander effect. The distribution of transplanted MSCs in mice and the tumor response to them could be monitored in real time by Fluc and Rluc imaging, respectively. The use of non-invasive imaging methods to detect disease progression and the distribution of transplanted cells in vivo will be beneficial to the clinical treatment of MSCs. Because molecular imaging can

visually describe biological processes in humans and other organisms, and can penetrate to cells and even molecules, it provides a non-invasive real-time monitoring method for the treatment of diseases. This holds a great potential for the treatment of disease.

In this paper, we explored the feasibility of engineered MSCs as gene delivery vectors for the treatment of colon cancer. MSCs and HT29 cells were transfected with the DF reporter (Fluc-HSV-ttk) and the DF reporter (Rluc-eGFP), respectively. Because Fluc and Rluc have different substrates, luciferase imaging can be used to simultaneously monitor the growth process of tumor and the transplantation efficiency of MSCs in vivo. Therefore, this traceable strategy provides a broader platform for new approaches to the treatment of diseases.

Previous studies have reported that MSCs could inhibit tumor growth by secreting cytokines such as interleukin, interferon-gamma and DKK-1/3.²⁶ In our study, engineered MSCs expressing the suicide gene ttk were used to systematically treat tumor model mice. We observed a decrease in the growth rate of tumors injected with MSCs, and the effect was more pronounced with the administration of

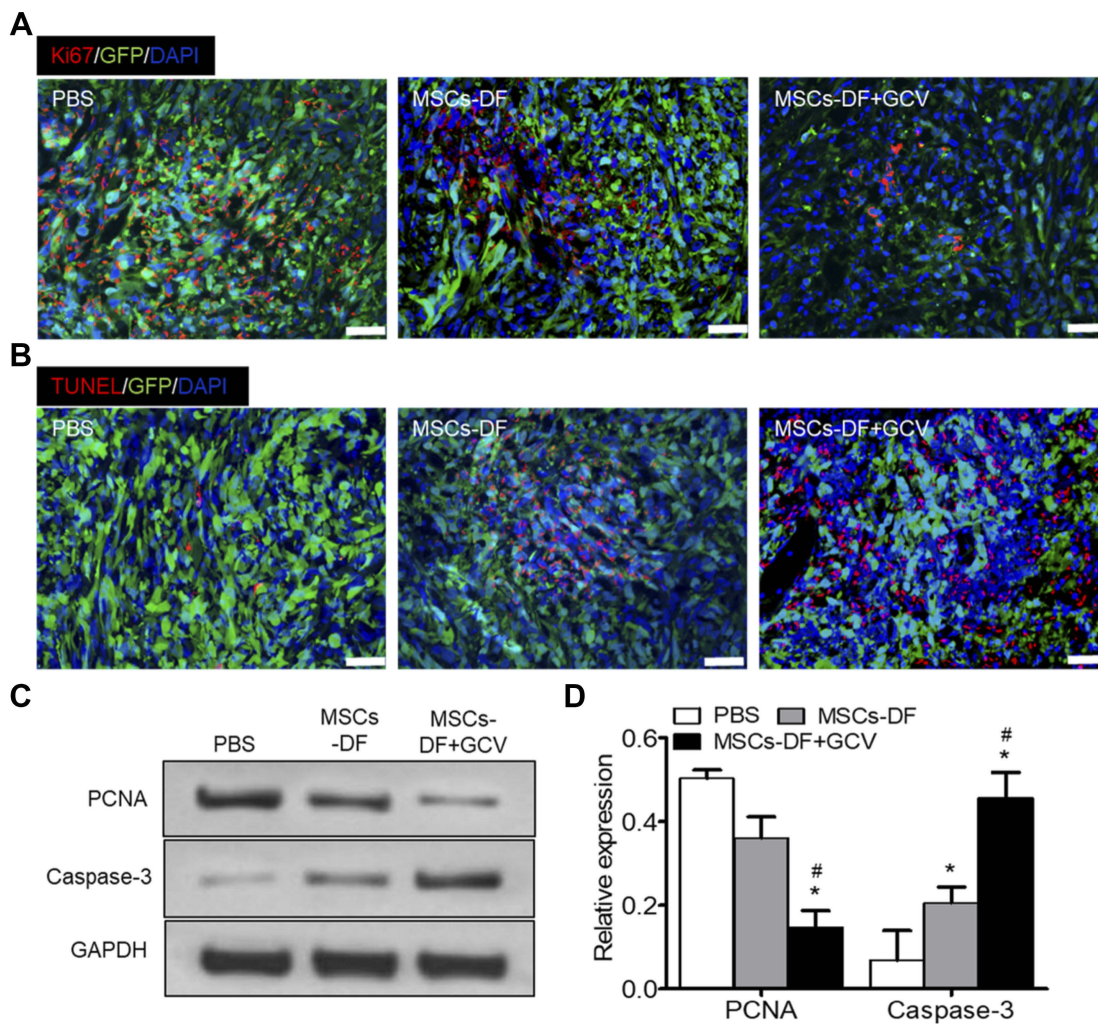


Figure 4 MSCs-DF reduced tumor proliferation and promoted apoptosis in vivo. **(A)** Proliferation protein was measured by the Ki67 assay. **(B)** The cell apoptosis was detected by the TUNEL assay. **(C)** Expression of proliferation marker PCNA and apoptosis marker cleaved Caspase-3 was analyzed by Western blotting. **(D)** Quantitative data of the expression of PCNA and Caspase-3. Data are expressed as mean \pm SEM. $n=6$. * $P<0.05$ versus PBS; # $P<0.05$ versus MSCs-DF. Scale bar, 100 μm . Experiments were performed in triplicate. MSCs-DF, hP-MSCs-DF; MSCs-DF+GCV, hP-MSCs-DF+GCV.

Abbreviations: MSC, mesenchymalstem cells; DF, double fusion; hP-MSCs, human placenta-derived MSCs; GCV, ganciclovir.

prodrug GCV, but this did not completely inhibit tumor growth. We found that the introduction of suicide genes into MSCs resulted in a tumor-specific prodrug transfer vector. Meanwhile, tumor growth may be inhibited by DKK-1 secreted by MSCs.²⁶

Considering the anti-tumor effect of hP-MSCs used in this study, it is possible to apply them in the treatment of tumor-forming conditions. We believe that different sources of MSCs, different cell delivery pathways and individual differences will be issues requiring special attention in cancer treatment in the future. Since MSCs are tumor-oriented, it will undoubtedly provide a new strategy for the treatment of tumors in the future. However, the role of MSCs in tumor microenvironment is so complex that it is difficult to show the specific role of

different sources of MSCs in different tumor models. Therefore, the specific role of MSCs in tumor microenvironment needs further extensive research in the future.

Conclusion

In summary, the results of this study provide data for the further development of MSCs as a carrier for targeted tumor therapy. The biological properties of engineered MSCs-DF combined with appropriate transgenic/prodrug may produce highly effective tumor cytotoxicity and may be used in the treatment of tumors in vivo. These cells possess many of the characteristics necessary for optimal cell delivery, which may prove beneficial in clinical studies.

Disclosure

The authors declare no conflicts of interest in this work.

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