LIGHT Delivery to Tumors by Mesenchymal Stem Cells Mobilizes an Effective Antitumor Immune Response

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Abstract

Bone marrow–derived mesenchymal stem cells (MSC) have been shown to home into tumor tissues, where they promote tumor growth and suppress immune rejection. In this study, we tested whether MSCs engineered to express the immune stimulating factor LIGHT, a member of the TNF superfamily, could induce tumor regression. Using in vitro and in vivo migration assays, we found that LIGHT-expressing MSCs (MSC-L) displayed a strong tropism for tumor tissues. MSC-L treatment activated the LIGHT-signaling pathway, effectively organizing a potent antitumor immune response that stimulated an influx of T cells and inhibited tumor growth in vivo. CD4 T cells were found to play a role in the induction phase of the immune response, and CD8 T cells were shown to be essential for the effector phase. Together, our findings indicate that MSCs can effectively home into and deliver immune stimulating molecules to tumor tissues, thereby reversing the immune-suppressive environment, promoting antitumor immunity, and inhibiting tumor growth. Cancer Res; 72(12); 2980–9. ©2012 AACR.

Introduction

Tumor tissues consist of cancer cells and stromal cells. These nontumor cells may provide suitable niche for tumor progression and act as barrier to block antitumor agents into tumor tissues (1). Recent studies have suggested that bone marrow–derived mesenchymal stem cells (MSC) were potential sources of tumor-related stroma (2–6). MSCs mainly reside within the bone marrow. They are characteristically able to differentiate into osteoblasts, chondrocytes, adipocytes, and other cells (7–9). Moreover, these cells can migrate into tumor and participate in tumor development (2–5, 10–12).

It is increasingly recognized that MSCs can exert immune suppression against host eradication of tumor. T-cell anergy can be induced by the lack of costimulatory molecules CD40, B7-1, and B7-2 on MSCs (10, 11). In addition, MSCs can induce immune tolerance via secretion of some soluble inhibitory factor (13). On the other hand, owing to their potent tropism to tumor tissues, MSCs could be ideal vehicles for targeted delivery of antitumor agents to tumor cells. It has been reported that the approaches could mediate tumor regression to certain extents (14–16). However, there were some limitations with these previous studies. For example, some of the research just only mixed with modified MSCs with tumors (15) or used xenograft animal model (16). Furthermore, there were rare reports investigating how to reverse tumor-suppressive microenvironments when MSCs used as vehicle.

LIGHT, an acronym for homologous to lymphotoxin, shows inducible expression, and competes with herpes simplex virus glycoprotein D for HVEM, a receptor expressed by T lymphocytes, is a member of the TNF family. LIGHT has a potent, CD28-independent, costimulatory role in T-cell activation (17). LIGHT can interact with lymphotoxin-β receptor (LTβR) and HVEM expressed on stromal cell and T cell, respectively (18). Constitutive expression of LIGHT can enhance the extravasation and homing of naïve T cells (19, 20). Moreover, recent data further confirmed the role of LIGHT in priming potent antitumor immunity (17, 21–25). For instance, we have showed that forced expression of LIGHT in the tumor could induce a massive infiltration of naïve T cells into tumor tissues. Activation of these T cells subsequently led to the rejection of established, highly progressive tumors at local and distal sites (22). Therefore, LIGHT is an excellent candidate molecule to target tumors by MSCs.

In this study, we investigated whether a stable expression of LIGHT in MSCs (MSC-L) can target delivering LIGHT into tumor tissues, thereby reverse tumor immunosuppressive environment via LIGHT priming immunity against tumors. Our data showed that MSCs efficiently delivered LIGHT into tumor tissues. We observed that MSC-L enhanced T-cell infiltrating into tumors and reversed the local suppressive environment, thereby efficiently control tumor in LIGHT-dependent adaptive immunity.
Materials and Methods

Mice and cell lines
Female aged 6 to 8 weeks of BALB/c mice were from Shanghai SLAC animal facility. All animal care and experiments were conducted according to Zhejiang University Animal Care Committee guidelines. The murine breast tumor cell line TUBO and human embryonic kidney–derived cell line AD293 were cultured in Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal calf serum (FCS).

Isolation, culture, and retroviral transduction of marrow MSCs
A female 6-week-old BALB/c mouse was sacrificed, and whole bone marrow was retrieved by flushing the bones with DMEM. All of the bone marrow cells were then cultured in DMEM with 15% FCS for 3 days. The cultured supernatant was harvested as MSCs conditional medium and the nonadherent hematopoietic cells were discarded (7, 9). The adherent cells were then washed 3 times with PBS, added 10 mL of DMEM with 10% FCS. When the cells grew to 60% confluence, the cells were transfected with LIGHT-expressing retrovirus vector.

For packaging LIGHT-expressing retrovirus, AD293 cells were plated with cell density about 50%. After 3 to 5 hours, the retrovirus was produced by transfecting AD293 with 250 μL Opti-MEM plus 37.5 μL of a solution made by mixing 15 μL LipofectAMINE (Invitrogen) with 7.5 μL of the packaging plasmid pAMpho and 15 μL of pSEB-LIGHT (22). Three to 5 hours later, the medium was discarded and replaced with 4 mL fresh complete DMEM. The retrovirus supernatants were collected at 36, 60, and 84 hours, respectively. The generated supernatant was used for infection of MSCs by adding 4 μL of pAMpho, 15 μL of pSEB-LIGHT (22) and 100 μL of the supernatant to MSCs. The generated supernatant was harvested as MSCs conditional medium and the nonadherent hematopoietic cells were discarded (7, 9). The adherent cells were then washed 3 times with PBS, added 10 mL of DMEM with 10% FCS. When the cells grew to 60% confluence, the cells were transfected with LIGHT-expressing retrovirus vector.

In vitro determination of MSC-L differentiation potential

To determine in vitro differentiation potential of MSC-L, the medium was replaced with osteogenic and adipogenic medium, respectively, when MSC-L were about 70% confluence. For the second round infection, the expression of LIGHT on MSCs was determined by flow cytometry. To block LIGHT activity in mice, LTβR-Ig (100 μg per injection) was given intraperitoneally at the indicated time as described previously (22).

Measurement of γ-IFN secreting T cells by ELISPOT assay

The performance of ELISPOT was done as described previously (29). Briefly, 4 × 10^5 spleen cells (responder cells) were added to each well, which had been precoated with 2.5 μg/mL rat anti-mouse γ-IFN (clone R4-6A2; BD-pharMingen). TUBO were added as APC over the spleen cells. The ratio of respond cells to APC was 10:1. After 48 hours of incubation, cells were removed and 100 μL of 2 μg/mL biotinylated rat anti-mouse-IFN-γ (clone XMG1.2; BD-PharMingen) were added to incubate for another 12 hours at 4°C, then unbound antibody were removed. Hundred microliters of 0.9 μg/mL avidin–horseradish peroxidase (BD-PharMingen) were added and incubated at 20°C for 2 hours. The substrate AEC was added. Three to 5 minutes later, the plates were washed and the spots were enumerated.

ELISA

After about 2 weeks of MSC-L treatment, tumor and spleen were collected and homogenized, the debris were spun down and supernatant were used for detection of IFN-γ (BD optEIA).
interleukin (IL)-6 (BD optEIA), IL-10 (BD optEIA), TGF-β (Abcam) with ELISA Kit, respectively.

**Histology**

Tumor tissues were collected at the indicated time, fixed in 10% neutral formalin, embedded in paraffin, and stained with hematoxylin and eosin (H&E), mAb to Ki67, or isotype Ab. Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining was done as protocol of the manufacturer. For CD31, CD4, CD8 staining, tumor tissues were embedded in OCT compound and frozen at -70°C. Frozen sections (5–7 μm) were stained with PE-conjugated antibodies to CD4 and to CD8 (BD PharMingen) and biotinylated goat antibodies to CD31 (Abcam), respectively.

**Results**

**MSC-L has multidifferentiation potential and strong tropism to tumor tissues**

MSCs have multidifferentiation capability and could home to tumor tissues (2, 28). To assess whether MSC-L still possess the above property, MSCs from 6-week BALB/c mice were stably transduced with retrovirus expressing LIGHT. LIGHT was readily detected by LTβR-Ig on the surface by flow cytometric analysis (Fig. 1A). After transduction with LIGHT, MSC-L adapted similar mesenchymal stromal cell–like morphology (Fig. 1B). Furthermore, mineral deposition was readily detected when MSC-L were stimulated with osteogenic medium, indicating that MSC-L have osteogenic potential (Fig. 1B). Meanwhile, the oil droplet was found in adipogenic medium, suggesting that MSC-L may differentiate into adipocytes (Fig. 1B). These results showed that MSC-L retained the multidifferentiation potential of MSC.

We next determined whether MSC-L exhibited any tropism to tumors. With in vitro Transwell experiments, we found that MSC-L possessed the potential of migration into tumors (Fig. 1C). For in vivo migration assay, we found that MSC-L may specifically migrate into tumor and mainly locate in tumor periphery (Fig. 1D and E and Supplementary Fig. S1B). In addition, the infiltration pattern of MSC-L in tumor was similar with MSC or MSC mock (Supplementary Fig. S2). Furthermore, LIGHT could be readily detected in tumor tissues after 2 weeks of MSC-L injection.
(Supplementary Fig. 1A). These findings suggested that MSC-L still can home and thereby deliver LIGHT into tumor tissues.

**MSC-L controls tumor growth efficiently**

To determine whether MSC-L can help host resistant against tumor, we first tested whether MSC-L could prevent tumor formation when mice were challenged with lethal dosage of TUBO cells at right flank after 2 weeks of $1 \times 10^6$ MSC-L inoculation at the left flank. We observed that MSC-L could efficiently provide protection against tumor (Fig. 2A and Supplementary Fig. S3A). We then analyzed the therapeutic potential of MSC-L. The mice were challenged with $4 \times 10^5$ of TUBO cells. Seven days later, MSC-L were inoculated into the other flank. In contrast to control groups, we found that MSC-L can effectively repress tumor-aggressive growth (Fig. 2B and Supplementary Fig. S3B).

**Tumor inhibition by MSC-L is not mainly due to tumor apoptosis or inhibition of angiogenesis and proliferation**

Tumor inhibition often ensues when cancer cells are counteracted by mechanisms such as growth arrest, impaired tumor vascularization, apoptosis, and immunosurveillance (30–33). To determine which mechanisms are involved in MSC-L–mediated tumor control, tumor histology was assessed after about 2 and 4 weeks of tumor inoculation, respectively. Ki67 was used to detect tumor cell proliferation. There were no difference of cell proliferation between MSC-L–treated group and control group (Fig. 3A and Supplementary Fig. S5A), which indicated that tumor cell growth arrest was not mainly involved in tumor control in this model.

To determine whether apoptosis may contribute to tumor inhibition in our experiments, TUNEL were done after about 2 and 4 weeks of tumor inoculation, respectively. Only marginal apoptosis was observed for different groups (Fig. 3B and Supplementary Fig. S5B).

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**Figure 2.** MSC-L controls tumor aggressive growth. A, for prophylactic protocol, BALB/c mice (8 per group) were injected with $1 \times 10^6$ MSC-L subcutaneously in the left flank and 13 days later, the mice were challenged with $4 \times 10^5$ TUBO in the contralateral flank. $P$ values were determined by one-way ANOVA test and log-rank test, respectively; $P < 0.001$. B, for therapeutic protocol, BALB/c mice (8 per group) were challenged with $4 \times 10^5$ TUBO in right flanks 7 days before $1 \times 10^6$ of MSC-L inoculation in the left flanks, MSCs or PBS was used as controls. Points, mean for each group of mice; bars, SD. $P$ value was calculated using one-way ANOVA test and log-rank tests, respectively; $P < 0.001$. 

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tested whether MSC-L could activate tumor-specific T cell secreting γ-IFN (Fig. 5A), which might in turn contribute to T-cell–mediated tumor control. Moreover, we observed that MSC-L may induce proinflammatory environment in local tumor tissues. After about 2 weeks of MSC-L injection, some cytokines in tumor tissues were detected with ELISA assay in therapeutic setting. As shown in Supplementary Fig. S4, the level of IFN-γ, IL-6 was largely increased, whereas IL-10, TGF-β decreased for MSC-L treatment. In addition, we found that in spleen, although IFN-γ level was enhanced to some extents for MSC-L–treated mice, but its level was still lower than in tumor tissues, which indicated that after migration into tumors, MSC-L may largely enhance local inflammation reaction.

Furthermore, we analyzed whether CD4 and CD8 T cells were essential in maintaining tumor control. Either in prophylactic protocol or therapeutic protocol, we observed that, in the induction stage before tumor challenge, CD4 T cells played an important role in tumor control. At this stage, deletion of CD4 T cells, but not CD8 T cells, could completely abort the MSC-L–induced antitumor immunity (Fig. 5B and C). Whereas in the effector stage, CD8 T cells were essential for tumor control, as deletion of CD8 T cells largely promoted tumor growth after short time of the continued inhibition (Fig. 5D and E); nevertheless, with CD4 deletion in effector stage, the host could still repress tumor growth (Fig. 5D and E).

In addition, for the tumor-free or dormant tumor-bearing mice (surgical removal of occult tumors before tumor rechallenge) treated with MSC-L, when rechallenged with $1 \times 10^6$ TUBO, they still resisted against tumor growth (Table 1 and Supplementary Table S1), which suggests the presence of immune memory for MSC-L–treated mice.

**Priming immunity of MSC-L was mainly dependent on LIGHT**

LIGHT has potent capability of priming T-cell activation independently of CD28 signaling (17). Our previous studies have shown that expression of LIGHT in the tumor can greatly enhance host resistance to tumor (22, 24). MSCs might have many molecules that are regulated after transfection of LIGHT. To investigate whether LIGHT is essential for MSC-L–mediated antitumor immunity, we first injected LTBR-Ig intraperitoneally to block LIGHT activity in vivo before MSC-L injection. Interestingly, in contrast to the mice without blockade of LIGHT, via consecutive 3 days injection of LTBR-Ig, the tumor posed with aggressive growth tendency (Fig. 6A and B). Next, we tested whether injection LTBR-Ig after MSC-L inoculation can still abolish MSC-L protection against tumor. At initial duration, for the mice receiving LTBR-Ig after about 1 week and 3 weeks of MSC-L inoculation, respectively, the host could continue to resist tumor growth for about 2 to 3 weeks, but after that time point, the tumors grew aggressively again (Fig. 6C and D), suggesting blockade of LIGHT activity could completely abolish the antitumor effect of MSC-L. We then tested whether the blockade of LIGHT activity could delete MSC-L priming T cells activation. Through ELISPOT assays for γ-IFN secretion of T cells, we observed that blockade of LIGHT

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Figure 3. MSC-L–mediated tumor regression is mainly not associated with tumor proliferation, tumor apoptosis, and angiogenesis. Mice tumor model were set up in the prophylactic and therapeutic protocol, respectively, as described in Fig. 2. At 4 weeks of TUBO challenge, tumor tissues were collected and immunohistochemistry was carried out with Ki67 staining (A); TUNEL assay (B), and CD31 detection (C).
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nearly completely inhibited the T cells producing γ-IFN (Fig. 6E). Clearly, these data present strong evidence that LIGHT signal pathway is essential for MSC-L priming antitumor immunity.

**Discussion**

Tumor microenvironment is immunosuppressive (35, 36) and tumor stroma is often referred as barrier blocking anti-tumor agents into tumors. Because MSCs can home to tumor, MSCs have been used as vehicle for tumor therapy (14, 16). However, owing to the immunosuppression of MSCs (3, 10, 11, 13, 37–39), the efficacy of the treatments would be largely compromised. How to circumvent its immunosuppression remains illusive. Herein, we have shown that expression of LIGHT on MSCs can break tumor barrier and prime antitumor immunity to control tumor growth. First, MSC-L can migrate and thereby target delivery of LIGHT into tumor; Second, the tumor control of MSC-L was not due to induction of tumor apoptosis, or inhibition of tumor angiogenesis and proliferation; Third, the infiltration of T cells and proinflammatory factor level were increased in tumor tissues with MSC-L treatment. Furthermore, we observed that CD4 T played a role in induction phase, whereas CD8 T was essential for effector phase. In addition, γ-IFN producing T cells were increased in lymphoid tissues and immune memory existed with MSC-L treatment. Fourth, LIGHT is essential for MSC-L priming antitumor immunity, suggesting the direct effect of LIGHT-expressing MSCs on tumor control. These findings indicate that MSC-L can circumvent the tumor immunosuppressive environment and may be used as vehicle for tumor treatment.

The ability of priming T-cell activation in tumors by MSC-L is an intriguing finding. MSCs have been broadly recognized as immunosuppressors (3, 10, 11, 13, 37–39). Nevertheless, recent studies suggested that, in specific conditions, MSCs might be able to behave as conditional APC to prime immune reactions. For instance, MSCs can cross-present soluble exogenous antigens to activate CD8 T cells (40). MSCs may also act as APC to prime CD4+ T-cell proliferation (41, 42). More recently, report showed that MSCs expressing ErbB-2/neu elicited full protective antitumor immunity in vivo (43). In line with the above findings, we observed that MSC-L can prime antitumor immunity to control tumor. Because tumor-targeted LIGHT not only can recruit DC and T cells into tumors but also has a potent, CD28-independent, costimulatory role in priming T-cell
activation (17); whereas MSCs usually lack costimulatory molecules CD40, B7-1 and B7-2, which may induce T-cell anergy when interacting with T cells (13, 37). In this regard, it remains interesting to investigate whether MSC-L, after migration into tumor, may directly act as APC via LIGHT as costimulatory molecule to prime immunity against tumor, so as to be distinct from the role of LIGHT itself directly priming potent antitumor immunity.

Tumor stromal cells are critical for tumor growth and immune monitoring. Reports showed that destruction of Tumor-free mice were directly rechallenged with 1 × 10^6 TUBO cells; mice bearing tumors were rechallenged with 1 × 10^6 TUBO cells after surgical removal of the tumor.

bOf the 8 mice treated with MSC-L, the tumors of 2 mice were maintained in dormancy.

Table 1  MSC-L prevents tumor growth and induces antitumor immune memory

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>First TUBO challenge</th>
<th>Incidence of tumor growth</th>
<th>Surgical removala and tumor rechallenge</th>
<th>Incidence of tumor growth %</th>
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<tbody>
<tr>
<td>1</td>
<td>PBS</td>
<td>4 × 10^5</td>
<td>8/8</td>
<td>1 × 10^6</td>
<td>6/6 100%</td>
</tr>
<tr>
<td>2</td>
<td>MSCs</td>
<td>4 × 10^5</td>
<td>8/8</td>
<td>1 × 10^6</td>
<td>8/8 100%</td>
</tr>
<tr>
<td>3</td>
<td>MSC-L</td>
<td>4 × 10^5</td>
<td>2/8 b</td>
<td>1 × 10^6</td>
<td>0</td>
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<tr>
<td>4</td>
<td>None</td>
<td>None</td>
<td></td>
<td>1 × 10^6</td>
<td>6/6 100%</td>
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tumor stromal cell was essential for eradication of established tumors (1, 44–47). However, the source of tumor stromal cells has not been well defined. MSCs have been suggested as one source of tumor stroma. Some reports showed that, after migration into tumor, MSCs can differentiate into carcinoma-associated fibroblasts (CAF) and pericytes (2, 3, 5, 6, 15). It has been observed that at least 20% of CAFs derived from MSCs (5). Recently, another report even showed that epithelial–mesenchymal transition-derived (EMT) cells might exhibit multilineage differentiation potential similar to MSCs (48). It has been increasingly recognized that tumor cells may experience EMT transition, especially in the case of metastasis. This study suggests that MSC-L likely survive for more than 14 days before tumor inoculation and could prime T cells infiltrating into tumor tissues, thereby reverse suppressive environment leading to tumor regression. Meanwhile, because LIGHT has potent priming immunity activity, overexpression of LIGHT may incur autoimmunity (17, 21). Accordingly, it remains to be determined whether expression of LIGHT on MSCs can prime anti-MSCs immunity and subsequently lead to destruction of MSCs, and even to destruction of tumor stroma and tumor cells when they experience EMT transition. Some studies have shown that MSCs can inhibit Kaposi sarcoma (KS) and some breast tumors. It was believed that MSCs inhibition of KS cells is mediated by a contact-dependent inhibition of Akt signaling (49), whereas MSCs inhibition of mammary carcinoma is via stimulating apoptosis by cleavage of PARP-1 and caspase-3 (50). In this study, our results support that MSC-L–mediated tumor control is not due to MSC-L direct contact inhibition of tumor cells. There were no apparently apoptosis or arrested cells in tumor tissues with MSC-L treatment. Instead, there were large number of T-cell infiltration into tumor tissues, and deletion of T cell may abolish antitumor effect of MSC-L. Furthermore, in the experiments with nude mice, treatment with MSC-L, MSCs, or PBS has no different effect on tumor growth. Presently, the complex

Figure 6. The antitumor immunity of MSC-L is mainly dependent on LIGHT. Mice were treated with MSC-L or MSCs in the prophylactic and therapeutic protocol, respectively. A and B, either in prophylactic protocol (A) or therapeutic protocol (B), blocking LIGHT with LTβR-Ig for consecutive 3 days before MSC-L inoculation can abort MSC-L protection against tumor. C and D, blockage of LIGHT after MSC-L inoculation also abolished MSC-L protection against tumor. In prophylactic protocol (C) or therapeutic protocol (D), blocking LIGHT with LTβR-Ig after about 1 week and 3 weeks of MSC-L inoculation, respectively, abrogated the protection of MSC-L against tumor growth. E, mice were treated with MSC-L in the prophylactic and therapeutic protocol, respectively. With 100 μg LTβR-Ig blockage of LIGHT signaling, 3 days later, spleen cells were isolated and used for ELISPOT assay. All experiments were repeated in triplicate. Columns, mean; bars, SE.
interaction of MSCs and tumors is poorly defined. Whether MSCs inhibit tumor growth may depend on specific conditions, which vary widely as a function of the source of MSCs and the tumor model used. Accordingly, how to decipher the mechanism of the interaction between MSCs and tumor cells will largely benefit MSCs as the vehicle for tumor treatment.

We previously tested that LIGHT, when expressed in tumor tissues, can prime potent antitumor immunity leading to the clearance of well-established tumor at local and distal sites (22). More recently, we further observed that targeting the primary tumor with Ad-LIGHT can generate CTL to effectively eradicate the metastasis tumor (24). In the present experiments, although we observed large numbers of T-cell infiltration into tumor tissues and T cells activation by MSC-L, we do not know why MSC-L cannot reject the established tumor, but only repress tumor aggressive growth and maintain host–tumor in an equilibrium state. Some previous works have supported the notion that, when MSCs were in the milieu of inflammation, MSCs might increase the production of large arrays of chemokines and immunosuppressive factors (13, 37). This indicates that MSCs may respond to inflammatory cytokines by attracting immune cells via chemokine secretion and thereby suppress these immune cells. Accordingly, although MSCs have been exhibited to act as APC to prime antitumor immunity in specific conditions, it remains unclear in our model whether MSC-L, when engraft in tumor tissues, still possesses some kind of immunosuppression, which would partly compromise the LIGHT-primed immunity.

Overall, our data showed that MSC-L could specifically migrate into tumor and control aggressive tumor growth by priming potent antitumor immunity. This study has addressed one efficient way to deliver immune stimulating factor LIGHT into tumors by MSCs and an approach of circumventing the immunosuppression of tumor environment via LIGHT. Because MSCs, as tumor stroma, play a pivotal role in tumor development and may compromise clinic treatment, this strategy has potential for translation to clinical application.

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

Authors’ Contributions
Conception and design: Y.-X. Fu, W. Fan
Development of methodology: W. Zou, T.-C. He, Y.-X. Fu, W. Fan
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): W. Zou, W. Fan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): W. Zou, J. Chang, Y.-X. Fu, W. Fan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Zheng, T.-C. He, Y.-X. Fu, W. Fan
Writing, review, and/or revision of the manuscript: T.-C. He, Y.-X. Fu, W. Fan
Study supervision: Y.-X. Fu, W. Fan

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