



The influence of antibody CD166 on the treatment of tumor and the immunological mechanism in mice bearing oral squamous cell carcinoma

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Background: This study aimed to investigate the influence of antibody CD166 on the inhibition of tumor and further investigate the influence on immune cells of tumor tissues in mice bearing oral squamous cell carcinoma (OSCC).

Methods: The xenograft model was established through subcutaneously injection of mouse OSCCs cells. Ten mice were randomly divided into two groups. The treatment group was treated with antibody CD166 and the control group was injected with the same volume normal saline. Hematoxylin and eosin (H&E) was used to confirm the tissue histopathology of xenograft mice model. Flow cytometry was used to detect the proportion of CD3⁺CD8⁺ T cells, CD8⁺PD-1⁺ cells and CD11b⁺Gr-1⁺ myeloid-derived suppressor cells (MDSCs) cells in the tumor tissues.

Results: After treatment with antibody CD166, the tumor volume and weight in xenograft mice model were significantly reduced. The result of flow cytometry showed that antibody CD166 showed no obvious influence on the proportion of CD3⁺CD8⁺ and CD8⁺PD-1⁺ T lymphocyte cells in the tumor tissues. In the antibody CD166 treatment group, the proportion of CD11b⁺Gr-1⁺ MDSCs cells in tumor tissues was 1.930%±0.5317%, which was significantly lower than that of the control group, 4.940%±0.3252% (P=0.0013).

Conclusions: Antibody CD166 treatment helped reduce the proportion of CD11b⁺Gr-1⁺ MDSCs cells, and produced obvious therapeutic effect on the treatment of mice bearing OSCC.

Keywords: Murine; oral squamous cell carcinoma (OSCC); antibody CD166; programmed cell death 1 (PD-1); myeloid-derived suppressor cells (MDSCs)

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Introduction

As estimated, over 300,000 cases of oral and oropharyngeal malignant tumors are diagnosed every year around the world, of which more than 90% are oral squamous cell carcinoma (OSCC) (1). OSCC is highly invasive and frequently

metastasizes to cervical lymph nodes (2). Although there are improvements in treatments, including surgery, radiotherapy, chemotherapy and other comprehensive methods, the survival rate is only about 60% (3). Nowadays, immunotherapy has become the focus of research around the world. With the

use of the monoclonal antibodies of epidermal growth factor receptor (EGFR) came to the clinical, the survival rate of a subset of the patients has improved (4). Immune checkpoint blockade eliminates inhibitory signals of T-cell activation, prevents T cell exhaustion, thus improving responsiveness to anti-tumor therapy (5). However, many patients still have primary or acquired resistance to these immunotherapies (6). Therefore, it is of great importance to develop new therapeutic methods in order to improve the survival rate of patients.

As a known fact, the number and function of T lymphocytes are significantly correlated with prognosis of patients in a variety of cancers (7). The T lymphocytes are divided into CD4⁺ and CD8⁺ subgroups, of which CD8⁺ T lymphocytes exert most striking effect on tumors (8). In some cases, the number and function of CD8⁺ T lymphocytes are correlated with immunosuppressive molecules, such as programmed cell death 1 (PD-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell immunoglobulin and mucin domain 3 (TIM-3), as well as immunosuppressive cells. PD-1 is mainly expressed in immune cells, including T lymphocytes. PD-1 inhibits immune responses by binding to programmed death-ligand 1 (PD-L1) on the surface of tumor cells (9). In malignant tumors, the increased expression of PD-1 and other inhibitory receptors can significantly inhibit the killing function of CD8⁺ T lymphocytes. Blocking expression of PD-1 with monoclonal antibodies could relieve the immunosuppressive effect on CD8⁺ T lymphocytes and increase the immune response to tumor cells (9).

Myeloid-derived suppressor cells (MDSCs) are a

population of immature myeloid cells that accumulate in patients with cancer and establish the pre-metastatic tumor microenvironment (TME) and play an important role in tumor metastasis (10). The surface markers of MDSCs were CD11b and Gr-1 in the tumor-bearing mouse model (11). In tumors, MDSCs mainly inhibit the proliferation and activation of effector T lymphocytes, leading to the failure of anti-tumor immune response and thereby promoting tumor progression (12,13). In addition to immunosuppressive effects, MDSCs can also reshape TME and affect tumor angiogenesis through non-immune effects, thus promoting tumor initiation and metastasis (14,15). Researchers nearly reached a consensus that MDSCs participated in the anticancer immune (16,17). Numerous cancer-related factors can also regulate the immunoregulatory potential of MDSCs in the TME.

CD166 is a type of I transmembrane glycoprotein, a member of the immunoglobulin superfamily, which can regulate the immune response and promote tumor growth, invasion and metastasis (18). Our previous studies have shown that CD166 is highly expressed in OSCC, which promotes the progression of OSCC through sustaining the stemness of tumor cells (19,20). It has also been reported that CD166 is ligand of cluster of differentiation (CD)6—a marker of T cells. Antibody CD166 block the binding of thymic epithelial cells to CD6-overexpressing kidney cells (21). Besides, CD166 promotes the nasopharyngeal carcinoma formation by activating the EGFR/ERK1/2 signaling (22). CD166 regulates melanoma cell adhesion molecule through a signaling activation of phosphatidylinositol-3-kinase (PI3K)/protein kinase B (PKB/AKT), thus maintaining transformative phenotype of hepatocellular carcinoma cells (23). CD166 is also reported to enhance hematopoietic stem cell (HSC) function by promoting the engraftment of HSC and the HSC-niche interactions, suggesting that CD166 expression can be modulated to enhance HSC function (24). This study aimed to analyze the effect of antibody CD166 on the growth of tumor and the immune indexes in mouse OSCC xenografts. We present the following article in accordance with the ARRIVE reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2704/rc>).

Highlight box

Key findings

- This study showed that antibody CD166 treatment produced obvious therapeutic effect on the treatment of mice bearing oral squamous cell carcinoma (OSCC).

What is known and what is new?

- Previous studies have shown that CD166 is highly expressed and promotes the progression of OSCC through sustaining the stemness of tumor cells.
- This study shows that treatment of antibody CD166 reduced the proportion of MDSCs—an immunosuppressive component in OSCC.

What is the implication, and what should change now?

- It suggests the feasibility of CD166 as an immunotherapeutic target for OSCC.
- Further studies with more numbers of mice are needed to detect how CD166 affect the proportions of MDSCs as well as the underlying mechanism.

Methods

Main reagent and antibody CD166

Mouse OSCC cell line SCC-7 was cultured in Dulbecco's

modified Eagle's medium (DMEM; Gibco, USA) supplemented with 10% fetal bovine serum (Gibco); 0.25% trypsin was used for cell passage. Antibodies BV421-CD45, FITC-CD3 (BD Pharmingen, USA), PE-CD8 (BD Pharmingen), APC-PD-1 (BD Pharmingen), FITC-CD11b (BD Pharmingen) and APC-Gr-1 (BD Pharmingen) were used to detect the proportion of immune cells of tumor tissues in mouse OSCC xenografts. Antibody CD166 (CST, USA) was used to inject into peri-tumor tissues in mice.

Establishment of mouse OSCC tumor-bearing model

The mouse OSCC cell line SCC-7 was seeded in DMEM medium containing 10% fetal bovine serum and cultured in a 5% CO₂ incubator at 37 °C. SCC-7 cells in the logarithmic growth phase were collected and counted, and the cells were diluted with serum-free fresh DMEM medium to a concentration of 10⁵.

C₃H mice were purchased from Beijing Vitonglihua Laboratory Animal Technology Co., LTD., License No. SCXK (Beijing) 2012-0001. Ten male C₃H mice aged 8 weeks were injected with 100 µL fresh DMEM medium containing 10⁵ SCC-7 cells subcutaneously in the left and right lower flanks of each mouse. The mice were in specific pathogen free (SPF) feeding conditions, with strict control of workflow, human flow, logistics and animal flow. Also, several supporting systems were applied, with air conditioning system, monitoring system, room differential pressure monitoring system.

Experiments were performed under a project license (No. SH9H-2022-A912-1) granted by institutional review board of the Shanghai Ninth People's Hospital, in compliance with institutional guidelines for the care and use of animals.

The therapeutic effect of antibody CD166 on tumor-bearing mice

Five days after the subcutaneous injection of SCC-7 cells, subcutaneous tumor formation was evident in C₃H mice. The mice were randomly divided into 2 groups, with 5 mice in each group. At this time, antibody CD166 was injected into tissues around the tumor in the experimental group, once every four days, 5 µg per tumor nodule. The control group was injected with the same volume of normal saline as the treatment group. The mice were observed once every four days. The general conditions, weight and tumor volume of the two groups were recorded. The painkiller was used to reduce the pain in mouse. When the body weight

of mouse reduced 20%, the mouse was sacrificed. With the treatment of antibody CD166, the conditions of C₃H mice were good. The mice were sacrificed by cervical dislocation on the 21st day after infection of SCC-7 cells. The tumor tissues were dissected, photographed and weighed for subsequent analysis.

Treatment of tumor tissues in tumor-bearing mice

After C₃H mice were sacrificed, subcutaneous tumors tissues were separated, with connective tissues removed, washed in 1× phosphate buffer saline (PBS) solution for three times. Part of the tissues were picked up and put in 10% formalin to make paraffin sections. The remaining tissue was cut up with sterile scissors to prepare single cell suspension.

Hematoxylin and eosin (H&E) analysis

The tumor tissues of C₃H mice were made into paraffin sections. The thickness of the sections was commonly 4 µm, performed serially. One section was randomly selected to perform the (H&E) analysis.

Preparation of single cell suspension and staining

About 1 mg/mL collagenase was added to the tumor tissues homogenates of C₃H mice. The homogenates were shaken, heated in a 37 °C incubator for 20 min, centrifuged. Then the supernatant was removed, washed and filtered in a filter net to make single cell suspension. The flow cytometry controls of CD3⁺CD8⁺ T cells was a fluorescence-minus-one (FMO) control and the cytometry controls of CD11b⁺Gr1⁺ MDSCs was isotype. The concentration of antibodies used (not the volume) for staining was 0.5 mg/mL. About 200,000 events were acquired every time.

- (I) Analysis of T lymphocytes: 0.5 µL FITC-CD3, 0.5 µL PE-CD8 and 0.5 µL APC-PD-1 antibodies were added to the single cell suspension, incubated for 15 min at room temperature in the dark, then washed with 2 mL PBS, centrifuged at 1,500 rpm for 3 min. The supernatant was removed and resuspended with 350 µL PBS for further analysis.
- (II) Analysis of MDSCs: 0.5 µL FITC-CD11b and 0.5 µL APC-Gr-1 antibodies were added to the single cell suspension, incubated for 15 min at room temperature in the dark, then washed with 2 mL PBS, centrifuged at 1,500 rpm for 3 min. The supernatant was removed and resuspended with

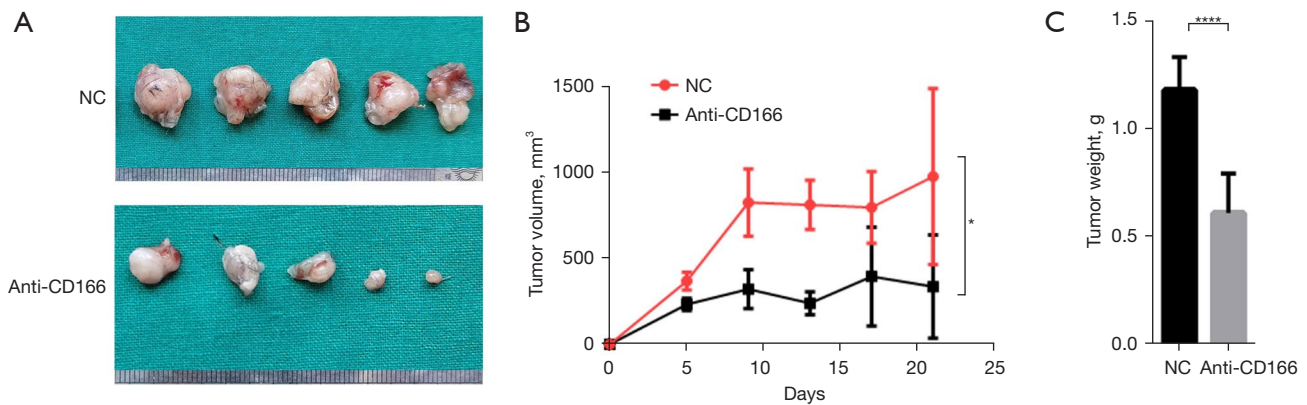


Figure 1 Antibody CD166 inhibited tumor growth in mice. The mouse SCC-7 cells were subcutaneous injection into mice to establish the transplantation tumor model of OSCC. (A) The mice were sacrificed at 21 days, and the tumors were isolated. (B) Tumor volume was recorded and charts were drawn (*, $P < 0.05$). (C) The isolated tumors were weighed and analyzed in the NC and the anti-CD166 group (****, $P < 0.0001$). NC, normal control; OSCC, oral squamous cell carcinoma.

350 μ L PBS for further analysis.

Statistical analysis

SPSS19.0 was used for statistical analysis in this study. The percentages of CD3⁺CD8⁺ T lymphocytes, CD8⁺PD-1⁺ cells and CD11b⁺Gr-1⁺ MDSCs in tumor tissues were compared between the control and the experimental groups by independent sample *t*-test. $P < 0.05$ was considered statistically significant.

Results

Antibody CD166 significantly inhibited the growth of tumor in mice

SCC-7 cells were injected into mice to establish the subcutaneous transplantation tumor model of OSCC. Antibody CD166 was injected into the tissues around the tumor in the experimental group from the 5th day, and the control group was treated with the same volume of normal saline. The weight and tumor volume of mice was recorded. At the 21st day, the mice were sacrificed and tumor cells were separated and photographed (Figure 1A). The results showed that the tumor volume of mice in the experimental group was significantly lower than that of the control group ($P < 0.05$) (Figure 1B). Then the subcutaneous tumors isolated from mice were weighed and calculated. The results showed that the average weight of tumors in the antibody CD166 antibody treatment group was 0.614 ± 0.058 g and that in the

control group was 1.182 ± 0.048 g, with significant difference ($P < 0.0001$) (Figure 1C).

Histopathological type of tissues in mice

The results of H&E staining showed that the subcutaneous tissues of mice in this experiment were OSCC tissues. The angiogenesis and leukocyte infiltration can be seen in the pictures of H&E staining. The intensity of leukocyte infiltration in the anti-CD166 group was larger than the normal control (NC) group (Figure 2).

The results of the flow cytometry analysis in tumor tissues

The mice were sacrificed on the 21st day after injection of tumor cells, and the fresh tumor tissues were cut into pieces respectively. The cells were gently filtered on a filter screen and resuspended as single cell suspension by PBS. The proportion of CD3⁺CD8⁺ T lymphocytes were detected by flow cytometry based on FMO controls. The cells were first gated by CD45, then gated by CD3, then CD8. The proportion of CD3⁺CD8⁺ was based on the CD45⁺ cells.

The results showed that the proportion of CD3⁺CD8⁺ T lymphocytes among the CD45⁺ cells in tumor tissues of control mice was $6.868\% \pm 0.875\%$, while $6.876\% \pm 1.379\%$ in the antibody CD166 treatment group, with no significant statistical difference between the two groups (Figure 3). These results indicated that antibody CD166 treatment had no significant effect on the numbers of CD3⁺CD8⁺ T lymphocytes in tumor tissues of mice.

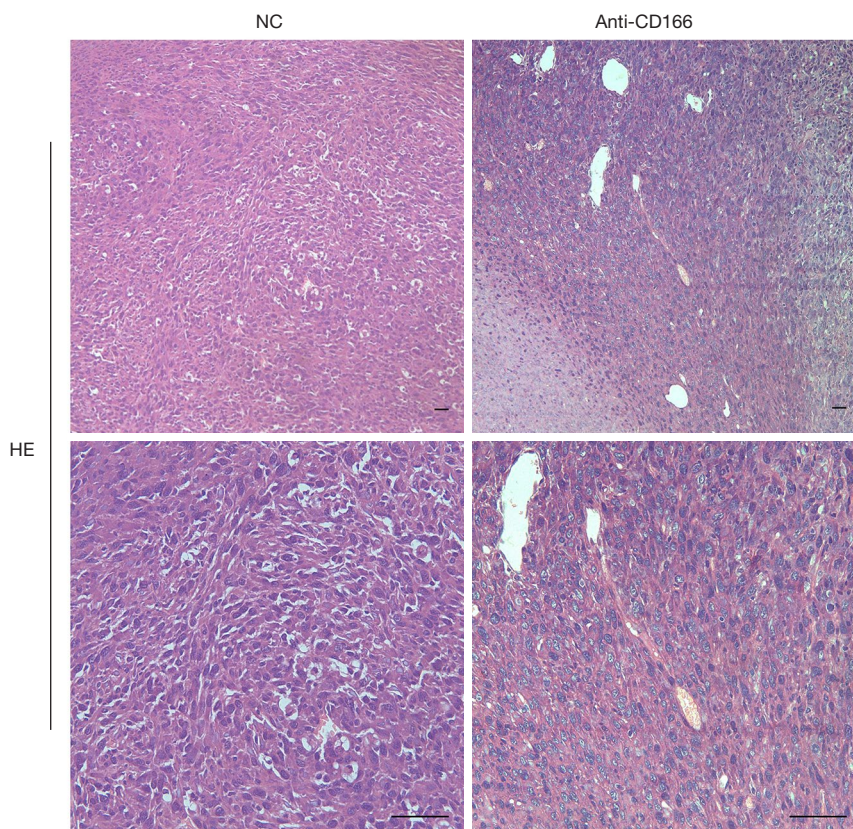


Figure 2 The H&E staining of subcutaneous tumor tissues of mice with microscope. Scale bar: 50 μ m. NC, normal control; H&E, hematoxylin and eosin.

Besides, the results showed that the proportion of CD8⁺PD-1⁺ T lymphocytes among the CD45⁺ cells in the tumor tissues of the control group was 79.26% \pm 5.655%, which showed no significant difference to that of the antibody CD166 treatment group (80.58% \pm 9.622%) (Figure 4). In order to assess the influence of CD166 on the proportion of CD8⁺PD-1⁺ T lymphocytes, the mean fluorescence intensity (MFI) of PD-1 was analyzed. The data showed that the MFI of PD-1 in tumor tissues of control mice was 7,762 \pm 258.4, which showed no significant difference to that of the antibody CD166 treatment group (7,311 \pm 777.3) (P=0.551). These results demonstrated that antibody CD166 treatment did not significantly reduce the number of CD8⁺PD-1⁺ T lymphocytes in tumor tissues of mice.

The proportion of CD11b⁺Gr-1⁺ MDSCs was analyzed by flow cytometry in fresh tumor tissues of sacrificed mice. The results showed that the proportion of CD11b⁺Gr-1⁺ MDSCs of the tumor tissues in the control group was 4.940% \pm 0.325%, which was significantly higher than that

in the antibody CD166 treatment group 1.930% \pm 0.532%) (Figure 5, P=0.0013). The results showed that antibody CD166 treatment could significantly reduce the number of CD11b⁺Gr-1⁺ MDSCs in tumor tissues of mice.

Discussion

CD166, a key factor in promoting cancer progression, has been confirmed to promote tumor progression in multiple myeloma (25). Our previous study have proved that CD166 promotes the growth of OSCC, and targeting CD166 might be a target for the treatment of OSCC (19). So, how does CD166 promote the malignant progression of OSCC? Could CD166 work as treatment target to inhibit tumor growth of OSCC? In this study, a C₃H mouse model of OSCC was established and treated with antibody CD166. PD-1/PD-L1 signaling is an important pathway in cancer progression and blocking PD-1/PD-L1 signaling is a focus in immunotherapy. Many drugs targeting PD-1 have been applied in clinical practice and are proved to be effective

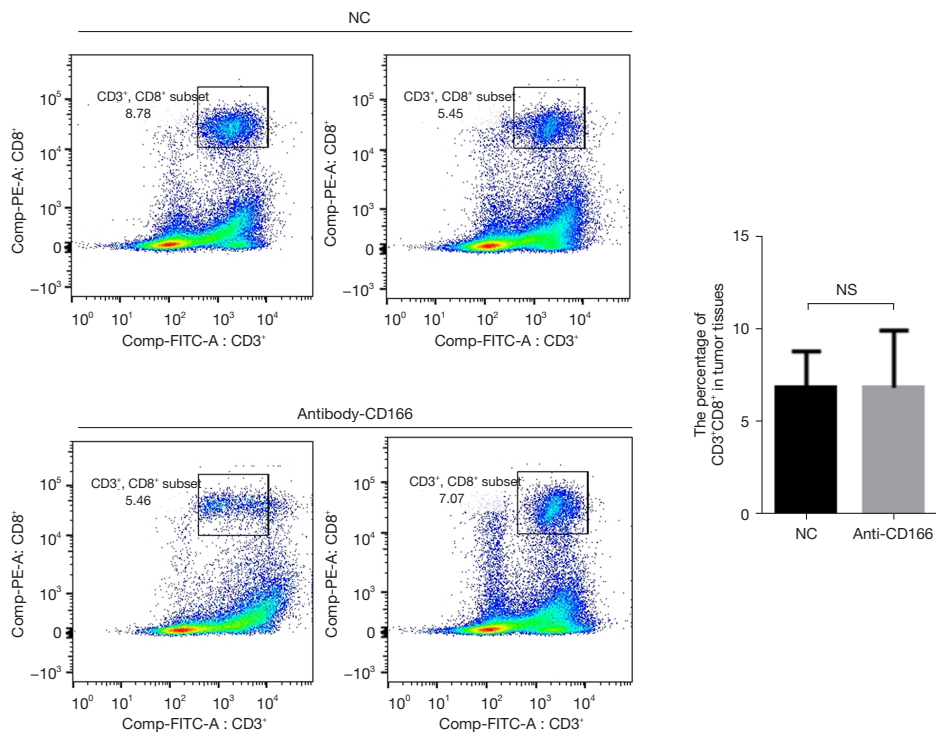


Figure 3 The proportion of CD3⁺CD8⁺ T lymphocytes in mouse tumor tissues was analyzed by flow cytometry in the NC and the anti-CD166 group. NS, P>0.05. NC, normal control; NS, nonsignificance.

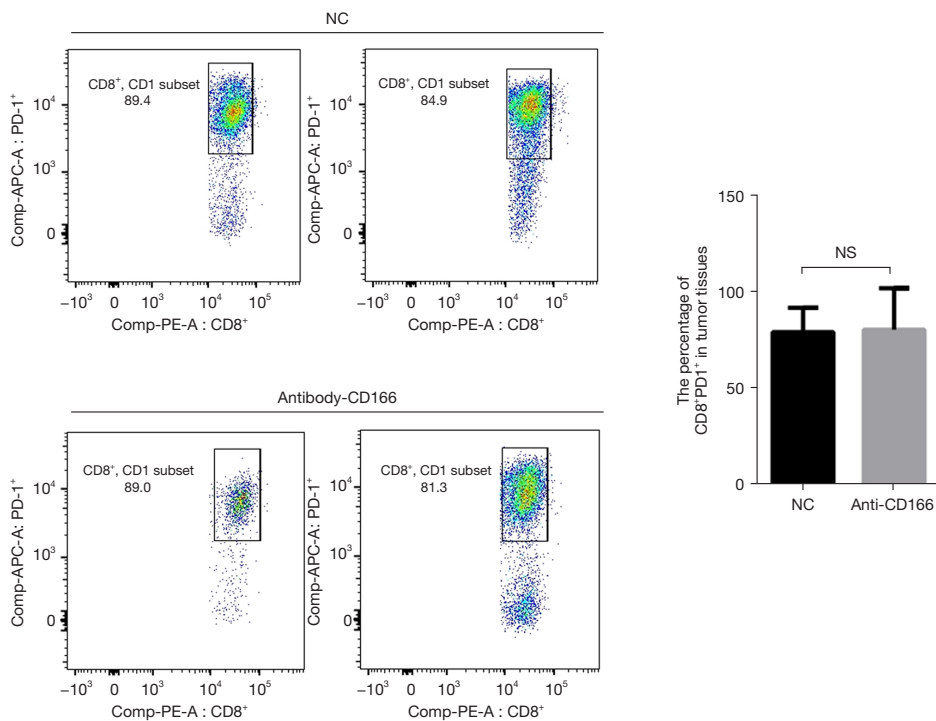


Figure 4 The proportion of CD8⁺PD-1⁺ T lymphocytes in mouse tumor tissues was analyzed by flow cytometry in the NC and the anti-CD166 group. NS, P>0.05. NC, normal control; PD-1, programmed cell death 1; NS, nonsignificance.

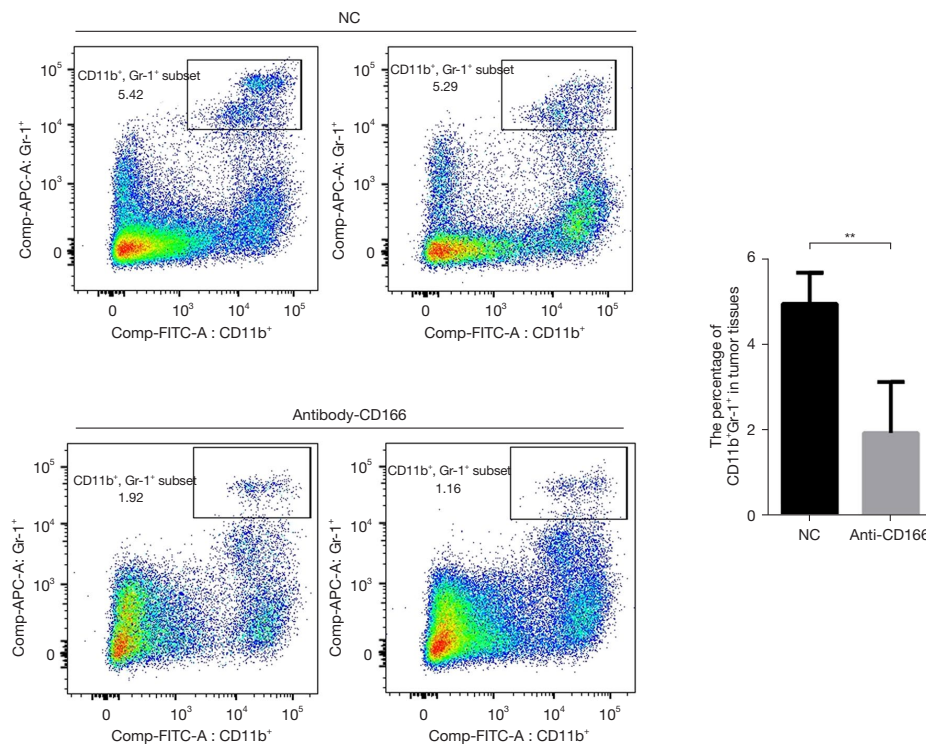


Figure 5 The proportion of CD11b⁺Gr-1⁺ MDSCs in mouse tumor tissues was analyzed by flow cytometry in the NC and the anti-CD166 group. **, $P < 0.01$. NC, normal control; MDSCs, myeloid-derived suppressor cells.

in prolonging the survival of patients with advanced head and neck squamous cell carcinoma (26,27). The results of the current study showed that the subcutaneous tumor volume of mice was significantly reduced with the treatment of antibody CD166, suggesting that CD166 might be a therapeutic target for OSCC. Besides, the proportion of CD3⁺CD8⁺ and PD-1⁺ T lymphocytes in tumor tissues of mice did not change significantly, which demonstrated that antibody CD166 might play an anti-tumor role by other mechanisms.

Antibody CD166 treatment reduced the immunosuppressive function of CD8⁺ T lymphocytes in the mice bearing OSCC. Another focus is whether antibody CD166 treatment had an effect on other immune cells? This study demonstrated that the proportion of CD11b⁺Gr-1⁺ MDSCs in tumor tissues of mice was significantly decreased after antibody CD166 treatment, suggesting the inhibitory effect of antibody CD166 on MDSCs. MDSCs inhibit the function of T lymphocytes by producing inducible nitric oxide synthase (i-NOS) and immunosuppressive cytokines, such as TGF- β and IL-10. Inhibition or elimination of MDSCs can increase the immune response to PD-1 in

squamous cell carcinoma or adenocarcinoma (28). In this study, the proportion of MDSCs in tumor tissues of mice significantly reduced after antibody CD166 treatment, which confirmed the immunosuppressive effect of MDSCs in OSCC. These results also suggested the feasibility of CD166 as a treatment target in the immunotherapy OSCC.

However, there are also some limitations in this study. First, the study was of small sample size with only 5 mice in each group. Second, this study only analyzed the proportions of CD3⁺CD8⁺ T lymphocytes, PD-1⁺CD8⁺ T lymphocytes and CD11b⁺Gr-1⁺ MDSCs in tumor tissues by flow cytometry, without exploring the underlying mechanism. Therefore, further studies with more numbers of mice are needed to detect how CD166 affect the proportions of MDSCs as well as the underlying mechanism.

Conclusions

This study demonstrated the anti-tumor effect of antibody CD166 in the subcutaneous tumor-bearing mouse model of OSCC. Besides, treatment of antibody CD166 also

reduced the proportion of MDSCs—an immunosuppressive component, suggesting the feasibility of CD166 as an immunotherapeutic target for OSCC.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2704/rc>

Data Sharing Statement: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2704/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2704/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. SH9H-2022-A912-1) granted by institutional review board of the Shanghai Ninth People's Hospital, in compliance with institutional guidelines for the care and use of animals.

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