

The role and significance of VEGFR2⁺ regulatory T cells in tumor immunity

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Abstract: Tumor development is closely related to angiogenesis, and VEGFR2 plays an important role in tumor angiogenesis. It is broadly expressed in the blood vessels, especially in the microvessels of tumor tissues. Furthermore, VEGFR2 is detected on the surface of the cell membrane in various immune cells, such as dendritic cells, macrophages, and regulatory T cells (Tregs). Tregs, which are one of the key negative regulatory factors in tumor immune microenvironments, show high-level expression of VEGFR2 which participates in the regulation of immunosuppressive function. VEGFR2⁺ Tregs play a potent suppressive role in the formation of immunosuppressive microenvironments. A large number of reports have proven the synergistic effects between targeted therapy for VEGFR2 and immunotherapy. The depression of VEGFR2 activity on T cells can significantly reduce the infiltration of Tregs into the tumor tissue. Targeted therapy for VEGFR2⁺ Tregs also provides a new choice for the clinical treatment of malignant solid tumors. In this paper, the role and significance of VEGFR2⁺ Tregs in tumor immunity in recent years are reviewed.

Keywords: anti-angiogenesis, tumor immune escape, tumor microenvironment, antitumor immunity, regulatory T cell, VEGFR2

Introduction

Since the conception of tumor angiogenesis was brought up,¹ the role of tumor angiogenesis has drawn increasing interest in the process of tumorigenesis. The members of the vascular endothelial growth factor (VEGF) family, including VEGF-A, VEGF-B, VEGF-C, and VEGF-D, and placental growth factor participate in the formation of angiogenesis. VEGF-A plays a central role in inducing tumor angiogenesis. It mainly binds to three different tyrosine kinase (TK) receptors: VEGFR1 (Flt-1), VEGFR2 (Flk-1, KDR), and VEGFR3. VEGFR2 is the most promising target among all the receptors. It contains four structural areas: an immunoglobulin-like domain in its extracellular region, a transmembrane region, membrane TK region, and the downstream carboxyl terminal parts, which cause cellular proliferation, migration, and survival.

Recently, there has been an emergence of many targeted drugs, like EGFR inhibitor, tyrosine kinase inhibitor (TKI), monoclonal antibodies, and so on. Many TKIs like sunitinib and sorafenib can inhibit tumor growth via blocking VEGFR1, VEGFR2, and VEGFR3.² Clinical studies showed that VEGFR-targeting drugs improve the immune status of patients with solid tumors by preventing tumor angiogenesis as well as reducing the number of Tregs in the immune microenvironment.^{3,4} Therefore, further exploration of VEGFR2⁺ Tregs will deepen our understanding of the mechanism on the combination of anti-angiogenic therapy and tumor immunotherapy.

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Tregs and tumor angiogenesis

Regulatory T cells (Tregs), known as classic CD4⁺CD25⁺ Tregs, have attracted great attention in immunology research and account for 5%–10% of the total T cells. Forkhead box p3 (Foxp3) is a critical transcriptional factor that regulates their proliferation and functions.⁵ The classic subtype is extensively divided into two categories: the natural regulatory T cells (nTregs), differentiated from the thymus, and the induced regulatory T cells (iTregs), induced by antigens or other cytokines such as TGF- β .⁶ Since VEGFR2 is detected in Tregs,⁷ VEGFR2⁺ Tregs were put forward as a new subset of Tregs that have high immunosuppressive activity in tumor immune microenvironment (TME). Studies have shown that there is an increased percentage of Tregs in lymphocytes and in tumor tissues.^{8–11} Additionally, patients with high levels of tumor-infiltrating Tregs exhibit poor clinical prognosis for a number of tumors.¹²

Tregs affect angiogenesis to a certain extent in the TME. It is generally believed that Tregs promote tumor angiogenesis via inhibiting the secretion of cytokines and chemokines, such as tumor necrosis factor- γ , interferon (IFN)- α , CXCL9, CXCL10, and CXCL11.¹³ With an increase in the number of surface molecules such as neuropilin-1 (NRP-1), VEGF, especially VEGFR2 found in VEGFR2⁺ Tregs,¹⁴ itself can synthesize and secrete angiogenic factors that directly regulate tumor angiogenesis.¹⁵ The influence of angiogenesis on Tregs should also be noted. Tumor vascular endothelial cells secrete inhibitory factors such as TGF- β and VEGF. TGF- β can induce phenotype conversion from CD4⁺ Foxp3⁺ T cells to CD4⁺ Foxp3⁺ T cells. VEGF inhibits the differentiation of dendritic cell (DC) precursor cells into mature DC cells¹⁶ and promotes the accumulation of myeloid-derived suppressor cells (MDSCs), Tregs, and tumor-associated macrophage cells.^{17–19} In the mouse model of metastatic colon cancer, VEGF plays a vital catalytic role in accumulating Tregs at the tumor tissue by combining with VEGFR2 or NRP-1.²⁰

There is growing evidence that targeting Tregs to decrease their ratio and attenuating their suppressive activity can enhance the antitumor immune response.^{39,46} Therefore, eliminating Tregs is an important stage in tumor therapy. However, due to the lack of specific tools to target these cells, systemic depletion of Tregs with anti-CD25 antibodies or anti-Foxp3 antibodies may result in autoimmune diseases accompanied with a depletion of activated effector T cells.

Today, multiple anti-angiogenic drugs are available that block some of the signal pathways like VEGF/VEGFR2 axis to reduce the number and function of Tregs. They could also

reduce the expression of interleukin (IL)-10 and TGF- β in TME.^{21,22} Simultaneously, a large number of randomized controlled clinical studies showed that anti-angiogenic drugs and immunotherapy were synergistic. In an advanced mouse melanoma model,²³ tumor-targeted delivery of sunitinib base enhances vaccine therapy for advanced melanoma by increasing the cytotoxic T-cell infiltration and decreasing the number and percentage of MDSCs and Tregs in TME. A clinical experiment which combined ipilimumab (an anti-CTLA4 antibody) and bevacizumab (an anti-VEGF antibody) indicated promising initial efficacy in melanoma patients.²⁴

In recent years, it has been indicated that amelioration of the immunosuppressive microenvironment by the anti-angiogenic agents is related to VEGFR2 on the surface of Tregs.⁷ The expression of VEGF on Tregs is dependent on the expression of Foxp3 and participates in the proliferation and functional regulation of Tregs.²⁵ In addition, it has been reported that Tregs synthesize and excrete VEGF in the surrounding environment, and thus control tumor angiogenesis and tumor cell proliferation directly.¹⁵ Considering the important role of VEGFR2⁺ Tregs in the tumor microenvironment, they have become a hotspot in tumor immunity at present.

The original mechanism and clinical significance of VEGFR2⁺ Tregs

Although the role of VEGFR2⁺ Tregs in various tumors remains largely unknown, further studies by Suzuki et al revealed that VEGFR2⁺Foxp3⁺CD4⁺ T cells can be found in ascites derived from pancreatic, ovarian, gastric, and lung cancers.⁷ The expression of VEGFR2 on Foxp3^{high}CD4⁺ T cells is more than on Foxp3⁺CD4⁺ T cells.

At present, there are some possible mechanisms to explain the increase of VEGFR2⁺ Tregs in tumor tissue: 1) TME or tumor-infiltrating macrophages release some cytokines to promote the production of VEGFR2⁺ Tregs, for instance, tumor cells secrete TGF- β , which induces VEGF-A secretion and can thus augment the number of VEGFR2⁺ Tregs.^{7,11} 2) The transition from VEGFR2⁺ T cells to VEGFR2⁺ T cells and the amplification of VEGFR2⁺ T-cell subsets in the microenvironment. Gavalas et al detected VEGFR2 on the surface of CD3⁺ T cells,²⁶ and Mor et al found that hypoxia induced the expression of VEGF and VEGFR in T-cell lines.²⁷ 3) Foxp3⁺VEGFR2⁺ Tregs may be differentiated from the thymus and induced in the peripheral blood. According to Suzuki et al's experiment,⁷ Foxp3⁺VEGFR2⁺ T cells were discovered in thymus, which suggested that Foxp3⁺VEGFR2⁺ T cells may be naturally generated.

4) Factors influencing the expression of Foxp3 may have an impact on the expression of VEGFR2. Ziogas et al²⁸ verified that VEGFR2 exists only in Foxp3⁺ Treg cells, and the results suggested that 50% Foxp3⁺ Tregs express VEGFR2 in the peripheral blood of healthy people, that only 30% Foxp3 Tregs express VEGFR2 in tumor patients, and that Foxp3 was positively correlated with VEGFR2. Sunitinib impedes the conversion of CD4⁺Foxp3⁻ to CD4⁺Foxp3⁺T lymphocytes in malignant melanoma mice.⁷

Tumor-infiltrating Foxp3⁺ Tregs play an important role in the prognosis of colonic carcinoma and gastric cancer;^{29,30} VEGFR2 secreted by tumor cells is closely related to the prognosis of liver cancer,³¹ renal cell carcinoma,³² and non-small-cell lung cancer (NSCLC).³³ The expression of VEGFR2 in NSCLC was unrelated to gender, age, and pathological type, but was positively associated with lymph node metastasis, clinical stage, and tumor differentiation. Suzuki et al elucidated a significant correlation between Foxp3⁺VEGFR2⁺ T cells and disease-free survival (DFS) as well as overall survival (OS) in colon cancer.³⁴ The level of Foxp3⁺VEGFR2⁺T cells in the tumor tissue can be used as an independent predictor of cancer recurrence and survival time in colorectal cancer patients. However, whether VEGFR2⁺ Tregs can be used for clinical prediction and as a prognostic factor in other cancer patients still remains to be confirmed.

The role of VEGFR2 on Tregs

The effect of VEGFR2 on Tregs is mainly reflected on the proliferation and function of Tregs. VEGFR2 exerts function by binding to VEGF and regulating tumor angiogenesis. The influence of VEGF on the proliferation of Tregs is controversial. Goto et al confirmed that VEGF mediates an increase of Tregs in malignant pleural effusion.³⁵ Ziogas et al demonstrated that VEGF is released by T cells in ovarian cancer patients with ascites,²⁸ which directly inhibited T-cell activation by inducing the expression of VEGFR, which is in accordance with that reported by Gavalas et al.²⁶ However, whether VEGFR2 can directly regulate the proliferation of Tregs is still contentious.

Studies reveal that VEGFR2⁺ Treg has strong inhibitory effect on CD4⁺ T cells. Tregs release IL-10, TGF- β , and a small amount of IFN- γ in breast and pancreatic cancers, and these cytokines further participate in the production of Tregs.⁷ Whether VEGFR2⁺ Tregs exert inhibitory effect via releasing more types of or a larger amount of immunosuppressive factors is undefined. Roland et al found that IL-1 β and CXCL1 are relevant to immune cell infiltration after using

VEGFR2 inhibitors, which suggested IL-1 β and IL-6 may be an index to assess clinic prognosis after treatment with anti-VEGFR drugs.³⁶

In addition, it has been reported that VEGFR2 is expressed both on the surface and the nucleus of Tregs.⁷ Domingues et al affirmed that VEGFR2 translocates into the nucleus and regulates self-transcription by activating its own promoter.³⁷ The expression of VEGFR2 in the nucleus suggests that the molecular mechanism of tumor angiogenesis may require the specific activity of VEGFR2, and the nuclear VEGFR2 can enhance the tumor angiogenesis response.

Targeting VEGFR2⁺ Tregs enhances antitumor immune response

Recently, a number of approaches have been exploited to reduce Tregs or to impair their suppressive activity, such as cisplatin plus docetaxel chemotherapy (75 mg/m² cisplatin plus 30 mg/m² docetaxel on day 1 and day 8, every three weeks, 4 cycles), CD25-targeted antibody, immune checkpoint inhibition, and chemokine receptor blockade.^{38–40,47} Therapeutic targeting of VEGFR2⁺ Tregs connects angiogenesis with immunotherapy, which suggests that the anti-angiogenic drugs targeting VEGF/VEGFR2 can improve the tumor microenvironment via reducing Treg cells.

Angiogenesis inhibitors are primarily divided into two categories: monoclonal antibodies targeting VEGF/VEGFR2 and molecule inhibitors of tyrosine kinase (TKIs). Bevacizumab is a monoclonal antibody of VEGF-A, and it has been approved by the US Food and Drug Administration (FDA) for first-line treatment in metastatic renal cell carcinoma, metastatic colorectal cancer, and advanced NSCLC. Bevacizumab could specifically bind to the extracellular domain of VEGFR2 and further block VEGFR2-related signaling pathways. Studies indicated that bevacizumab inhibits Tregs in the peripheral blood of metastatic colorectal cancer patients.⁴¹

TKIs comprise sorafenib and sunitinib, the target of which includes VEGFR2. Sunitinib reduces the number of Tregs and MDSCs, and decreases the inhibitory effect of MDSC in patients with metastatic renal cell carcinoma.⁴² It also prevents Treg and MDSC infiltration around tumor cells.⁴³ Similarly, sorafenib significantly decreases the proliferation of Tregs in hepatocellular carcinoma⁴⁴ and renal cell carcinoma.⁴⁵

Multitargeted drug combination such as bevacizumab and TKI, or TKI targeting VEGF and NRP-1, has been proved to enhance clinical treatment. Cabozantinib and MVA/rF-CEA/TRICOM (antitumor vaccine immune stimulator)

reduce the number of Tregs and MDSCs, but increase CD8⁺ and CD4⁺ T-cell infiltration.⁴¹ Therefore, targeted therapy aimed at VEGFR2⁺ Tregs has a broad future outlook.

Summary and prospects

As one of the key immunosuppressive cells in tumor microenvironment, VEGFR2⁺ Tregs play a vital role in tumor immune evasion. Therapy targeting VEGFR2⁺ Tregs is of great significance to modify the TME. However, the mechanism of immune evasion by VEGFR2⁺ Tregs requires further exploration. Besides, the expression of VEGFR2 in other immune cells will also be a hotspot in the future research. Therefore, studying the role of VEGFR2⁺ Tregs in tumor immunity and taking appropriate treatment will benefit more patients with cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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