Review Article

Significance of peripheral blood Tregs in tumor: a narrative review

Ruihua Fang[1,2,3], Chubo Xie[1,2,3], Yudong Long[1,2,3], Chengcheng Zhang[1,2,3], Zhiyu Zhang[1,2,3], Lin Chen[1,2,3], Yi Wei[1,2,3]

[1]Department of Otorhinolaryngology Head and Neck Surgery, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China; [2]Institute of Otorhinolaryngology Head and Neck Surgery, Sun Yat-sen University, Guangzhou, China; [3]Guangzhou Key Laboratory of Otorhinolaryngology, Guangzhou, China

Contributions: (I) Conception and design: R Fang; (II) Administrative support: Y Wei; (III) Provision of study materials or patients: Z Zhang; (IV) Collection and assembly of data: C Xie; (V) Data analysis and interpretation: Y Long; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yi Wei, PhD. Department of Otorhinolaryngology Head and Neck Surgery, the First Affiliated Hospital, Sun Yat-sen University, 2nd Zhongshan Road 58#, Guangzhou 510080, China. Email: weiyi6@mail.sysu.edu.cn.

Abstract: Regulatory T cells (Tregs), a subgroup of T cells, regulate the autoimmune response with immunosuppressive functions. It plays an important role in suppressing inflammation and tumor cells to evade host immune surveillance. In recent years, Tregs has become a hot topic of research in tumor. Increasing evidence indicates that the proportion of Tregs increase in peripheral blood and tumor tissues, which is also closely associated to the tumor progression, surgery, chemotherapy and patients prognosis, although normally Tregs can maintain immune tolerance to self and prevent autoimmunity. What's more, the peripheral blood Tregs are closely associated with the clinicopathological factors of tumor patients, which involved in the metastasis and recurrence of tumors. Studies also demonstrate that Tregs may be largely responsible for attenuating antitumor immune responses in patients with cancer. However, the mechanisms by which Tregs suppress antitumor immunity remain unclear. Tregs in peripheral blood plays a major role in tumor immunity which closely related to the prognosis of patients. The detection of Tregs ratio in peripheral blood is expected to become an important weapon in clinical detection of tumor development, recurrence and prognosis of patients. Targeted regulation of Tregs production in peripheral blood may provide assistance for tumor immunotherapy.

Keywords: Regulatory T cells (Tregs); inflammation; tumor; peripheral blood

Received: 22 July 2020; Accepted: 15 December 2020; Published: 30 December 2020.
doi: 10.21037/aob-20-53
View this article at: http://dx.doi.org/10.21037/aob-20-53

Introduction

According to researches, tumor cells can escape the immune surveillance through inhibiting patients immune responses, and inducing an immunological tolerance, so that our immune system can't get rid of tumors. This is the main reason that many immunotherapies in cancer were failed. As we all knows, according to their developmental origins, Tregs can be classified into two major groups. One of which is designated as thymus-derived Treg (tTreg) cells because it develops in the thymus gland. Another develops when naive peripheral $CD4^+$ T cells become activated by antigen and environmental signals stimulation that promote Foxp3 expression and suppressive function (1). It is suggesting that Tregs accumulating in the peripheral blood of cancer patients can suppress immune antitumor responses and promote tumor progression (2). Moreover, it is well accepted that Tregs are directly associated with both poor survival outcomes and unfavorable disease characteristics in tumor.

Therefore, the proportion of Tregs in peripheral blood of patients has a crucial clinical value in the survival prediction. Here, we aimed to give a briefly review about the level of Tregs in peripheral blood and their relationship

with tumors. In the future, targeted therapy of Tregs may be expected to be a therapeutic strategy to improve the patients prognosis.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aob-20-53).

The proportion of Tregs in patient peripheral blood

There was a mounting body of evidence demonstrated that the number and proportion of Treg cells in peripheral blood were significantly increased in most tumors, such as colorectal cancer (3), gastric carcinoma (4), lung cancer (5), ovarian cancer (6), pancreatic cancer (7), breast cancer (8), liver cancer (9) and so on, compared with the normal control group. It was suggesting that the immune system of tumor patients was deficient. What's more, the proportion of Tregs in peripheral blood of benign and malignant tumors were different as well as. The proportion of Tregs in peripheral blood of ovarian cancer patients was significantly higher than that of benign ovarian tumors and normal healthy patients. Related studies found that the level of peripheral blood Tregs of serous adenocarcinoma patients was significantly higher than that in non-serous adenocarcinoma patients in ovarian cancer (10). $CD4^+CD25^+$ Tregs were highly expressed in the peripheral blood of patients with head and neck squamous cell carcinoma, which indicated that Tregs might inhibit the immune system in patients and promoted the development of carcinoma (11). Wolf *et al.* (12) showed the evidence of an increased of $CD4^+CD25^+$ regulatory T cells (Tregs) in the peripheral blood of patients with epithelial malignancies which might be considered as the design of immunomodulatory therapies such as dendritic cell vaccination.

The relationship between peripheral blood Tregs and clinicopathological factors of tumor

In clinical trial, metastasis is the most critical aspect of tumor progression. Tregs in the peripheral blood may well support cancer cells during metastasis. Importantly, when increased the numbers of Tregs in peripheral blood, the higher metastatic potential of Her-2/neu-positive cells happened, which suggested that it might be a potential role as a prognostic parameter (12). It was confirmed that the frequencies of Tregs in peripheral blood was closely related to patient clinicopathological parameters in tumor, which might participate in the process of tumor development (13). Hu *et al.* (14) showed that the frequencies of Tregs in peripheral blood were significantly higher in advanced-stage NSCLC patients than the patients with limited-stage NSCLC, which indicates that the Tregs in peripheral blood might be involved in the pathogenesis of NSCLC. Study also found that the frequency of Tregs in peripheral blood of postoperative patients with urothelial bladder cancer were decreased comparing to preoperative patients. The frequency of Tregs in peripheral blood of postoperative patients with urothelial bladder cancer were decreased comparing to preoperative patients. In the early stage of the tumor development (pTa-pT2), the higher level of tumor infiltration Tregs in peripheral blood were significantly positively associated with the larger tumor size. It was indicated that the Tregs ($CD4^+CD25^+Foxp3^+$) could stimulate immune tolerance and promote tumor progression, which might act as a novel prognostic biomarker in the clinical (15). In addition, study reported that the increased proportion of $CD4^+$ $CD25^+$ Tregs in peripheral blood were correlated with the clinical stage, pathological differentiation and lymph node metastasis (4). The proportion of peripheral blood Tregs in stage III-IV patients was significantly higher than that in stage I-II patients, as well as the pathological differentiation. What's more, the level of Tregs in peripheral blood of the patients with lymph node metastasis were increased than those without lymph node (16). All of the above studies revealed that the Tregs might be directly involved in tumor progression and its level in peripheral blood of the patients might be used as an indicator for treatment.

The peripheral blood Tregs is closely related to the poor prognosis and treatment

Growing evidence suggests that the increasing peripheral blood Tregs in patients with malignant tumors are associated with poor prognosis. Griffiths *et al.* (17) showed that the frequency of $CD4^+$ CD25 high T cells in HCC patients was significantly higher than in healthy donors. It also demonstrated that patients with higher Tregs frequency in peripheral blood were associated with poorer survival. The frequency of Tregs in peripheral blood of patients might vary when different anticancer treatments were used. As the study reported, the percentage of $Foxp3^{(+)}$ Tregs in $CD4^{(+)}$ T lymphocyte subsets of peripheral blood before surgical intervention were significantly higher than that in peripheral blood after surgery (18). Among the patients

with ovarian cancer undergoing surgery and chemotherapy, the patients with a higher percentage of Tregs in the CD4 cell population before chemotherapy had poorer long-term treatment outcomes, suggesting that assessment of Treg levels pre-chemotherapy could predict survival in ovarian cancer patient (10). In the process of tumor treatment, the frequency of peripheral blood Tregs plays a great significance role in the clinical efficacy and prognosis evaluation.

Conclusions

In summary, the proportion of Tregs in peripheral blood is upregulated in tumors which is associated with the tumor progression and clinicopathological factors. Reducing the proportion of Tregs in the tumor microenvironment is expected to be a more effective immunotherapy method to improve the patients prognosis.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at http://dx.doi.org/10.21037/aob-20-53

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aob-20-53). 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.

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doi: 10.21037/aob-20-53
Cite this article as: Fang R, Xie C, Long Y, Zhang C, Zhang Z, Chen L, Wei Y. Significance of peripheral blood Tregs in tumor: a narrative review. Ann Blood 2020;5:34.