The common goal of all living organisms is to sustain life. The human body serves as a host for many organisms to perpetuate their generations. Consequently, the human body is constantly exposed to invasion by external factors. A defense system is necessary to counteract these threats.

The immune system is a complex system that detects various foreign pathogens and develops different responses to defend the organism against these pathogens. Additionally, the immune system has developed various effector mechanisms to prevent autoimmunity and assist in tissue repair. It can activate many protective mechanisms against inflammatory diseases, tissue dysfunction and destruction, inflammation, and cancer. At the center of these mechanisms performed to protect the host are CD4+ regulatory T (Treg) cells.

Treg cells express high levels of CD25 together with the high-affinity interleukin (IL)-2 receptor alpha (α) chain and represent a subset of CD4+ T cells. They play a crucial role in maintaining immunological self-tolerance and immune homeostasis.

The regulatory functions of Treg cells also impact various other immune cells, including dendritic cells (DCs), macrophages, gamma/delta (γδ) T cells, neutrophils, and natural killer (NK) cells. Therefore, preserving a balanced and functional Treg population is crucial for preventing both autoimmune and chronic inflammatory diseases. Treg cells suppress abnormal immune responses against self-antigens and contribute to preventing autoimmune diseases. However, their limiting roles in immune responses against self-antigens can also lead to adverse outcomes.

Treg cells are characterized by the expression of the transcription factor forkhead box protein 3 (FoxP3), also known as Scurfin. According to research, FoxP3 is the best marker for CD4+ Treg cells in both mice and humans, although there are some differences between FoxP3 in humans and mice. Human FoxP3 has two isoforms, one encoding the full-length FoxP3 and the other encoding a short version of the protein lacking exon 2. However, the short form described in human FoxP3 is not present in murine CD4+ Treg cells. Another difference between human and mouse FoxP3 is that in human CD4+ T cells, FoxP3 expression......
REGULATORY T CELLS AND CANCER

The effects of Treg cells on cancer are complex. However, numerous studies have reported that the infiltration of Treg cells into various tumor tissues supports tumor progression by limiting anti-tumor immunity and promoting tumor immune escape. Treg cells are highly proficient in suppressing immune responses in vitro functional experiments. The infiltration of a large number of Treg cells to tumor tissues is generally associated with a poor prognosis in many cancer types, including melanoma, non-small cell lung, gastric, hepatocellular, pancreatic, renal cell, breast, and cervical cancers. At the same time, Treg cells in the tumor microenvironment encompass heterogeneous cell subsets expressing different immunosuppressive molecules that support tumor progression. In other words, Treg cells induce an immunosuppressive microenvironment, which is a significant barrier to successful tumor immunotherapy. However, this situation varies in some cancer types.

In certain cancers such as colorectal carcinoma, Treg cells suppress bacteria-induced inflammation, promoting carcinogenesis and creating a beneficial condition for the host. Here, high levels of Treg cells are associated with a positive prognosis. It is believed that this association arises from the known ability of Treg cells to suppress general inflammation, triggering cell proliferation and metastasis. Therefore, the direct correlation between a high percentage of Treg cells and patient survival prognosis requires further investigation. The accumulation of Treg cells in the tumor microenvironment and the role of antigen specificity in this process are crucial aspects to consider. The dual role of Treg cells in cancer and their role in cancer development significantly depends on both the type and location of the tumor.

Increase of Treg Cells in the Tumor Microenvironment

The infiltration of Treg cells into the tumor microenvironment occurs through chemokines. For example, in breast cancer, this process involves the binding of the chemokine receptor CCR4 expressed by Treg cells to the ligand CCL22 secreted by many tumor cell types.

Transforming growth factor-beta, a cytokine generally produced by tumor cells induces the differentiation and activation of Treg cells. Additionally, IL-10 also plays a role in the induction and differentiation of Treg cells. The TGF-β has a significant role in the induction and maintenance of FoxP3 expression, suppressive function, and homeostasis in peripheral CD4+ CD25+ Treg cells.

Tumor cells not only produce IL-10 or TGF-β but also induce the secretion of TGF-β/IL-10 by immature myeloid DCs or immature myeloid suppressor cells. This leads to the formation of CD4+ CD25+ Treg cells.

At the same time, it is thought that some naturally occurring CD4+ CD25+ Treg cells directly produced by the thymus may have cross-reactivity with antigens expressed by cancer cells. As a result, these types of Treg cells accumulate in tumor areas. These cells are significantly different from conventional T cells that penetrate the tumor. However, there is still no
definitive information on whether these antigens are recognized only by these Treg cells or if recognition is shared by helper CD4+ T cells. Additionally, another reason for the high percentage of Treg cells in the tumor microenvironment is speculated to be the transformation of peripheral CD4+ CD25+ naive T cells into Treg cells.\textsuperscript{17}

**TARGETING TREG CELLS IN CANCER IMMUNOTHERAPY**

Evading the immune system is a distinctive feature of cancer cells. Strategies are being developed to prevent this phenomenon and to eliminate tumor cells. Treg cells play a crucial role in shaping the tumor microenvironment to prevent optimal function of effector cells, prompting increased research on the manipulation of Treg cell reduction or suppressive functions.\textsuperscript{9} Studies indicate that systematic depletion of Treg cells enhances the anti-tumor response.\textsuperscript{13} However, systemic depletion of Treg cells can lead to autoimmunity. Consequently, immune system cells recognize their own self-antigens as foreign, activating an immune response against these antigens. This process results in the elimination of self-antigens, leading to the development of autoimmune diseases.

With the implementation of specifically targeting Treg cells by administering CD25 monoclonal antibody (mAb), the immunological unresponsiveness against tumor cells has been eliminated.\textsuperscript{18} Simultaneously, it induced the spontaneous development of tumor-specific CD8+ effector T cells and NK cells. However, the depletion of Treg cells has led to cross-reactive tumor immunity against tumors of various origins, and independent of this depletion, the application of CD25 mAb has not resulted in any tumor regression. Following the administration of this process, the number of Treg cells tends to increase over time, and the capacity to generate an anti-tumor response gradually diminishes.

Various cell surface molecules, including chemokine receptors such as CCR4 specifically expressed by effector Treg cells, can be candidates for consumption by monoclonal antibodies that specifically target effector Treg cells.\textsuperscript{13} An important application in immunotherapy involves the use of immune checkpoint inhibitors (ICI), which are antagonistic antibodies blocking crucial immune regulatory molecules (checkpoint molecules) such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4).\textsuperscript{10} It is known that human CTLA-4 antibodies provide long-term protection against melanoma. These antibodies are believed to block negative signals from B7-CTLA-4 interactions to increase the activation of naive T cells, thereby leading to tumor rejection. Additionally, anti-CTLA-4 antibodies selectively induce the depletion of Treg cells in the tumor microenvironment. Therefore, anti-CTLA-4 antibodies induce tumor rejection. The first anti-CTLA-4 antibody for melanoma treatment, Ipilimumab, has shown significant and lasting effects. According to the checkpoint blockade hypothesis, anti-CTLA-4 antibodies block the B7-CTLA-4 signal in peripheral lymphoid organs, supporting the activation of naive T cells and resulting in tumor rejection. However, the accuracy of this hypothesis has not been proven.\textsuperscript{19} The B7 ligands are common stimulatory molecules expressed on the cell surface, and therefore, it is recommended to conduct studies on whether Ipilimumab effectively blocks B7-CTLA-4 interactions under physiological conditions.

As a result of studies on this subject, it has been found that blocking the B7-CTLA-4 interaction is unnecessary for the immunotherapeutic effect of anti-CTLA-4 antibodies. It has been noted that the idea that anti-CTLA-4 antibodies induce tumor rejection by promoting T cell activation in lymphoid organs is not accurate. As studies continue, it has been observed that mouse anti-CTLA-4 antibodies induce tumor rejection through the selective depletion of Treg cells in the tumor microenvironment. The results obtained with mouse anti-CTLA-4 antibodies are similar to the results obtained with human anti-CTLA-4 antibodies.\textsuperscript{16-19}

An important barrier to the effectiveness of ICI immunotherapy is tumor resistance due to the immunosuppressive nature of the tumor microenvironment, and Treg cells are among the most abundant suppressive cells in the tumor microenvironment. The primary reason for Treg cells representing a direct target of ICI immunotherapy is the abundant expression of checkpoint molecules such as CTLA4, PD1, and LAG3.\textsuperscript{18} With the widespread use of ICI for cancer treatment, an increase in immune-related adverse events that pose a serious threat is likely. This challenge has prompted the consideration of ways to maintain immune homeostasis after ICI therapy. Therefore, understanding the role of Treg cells is crucial for triggering an effective anti-tumor response while maintaining immune homeostasis, and ongoing research aims to achieve this goal.\textsuperscript{20-23}

Efforts in cancer immunotherapy are focused on eliminating the suppressive functions of Treg cells.
One approach to this issue involves targeting CD25+ Treg cells with a specific antibody or ONTAK (an IL-2 toxin fusion protein). However, this approach may not efficiently eliminate Treg cells or may result in the removal of both Treg cells and activated effector cells. The reason for this is that the CD25 marker is not specific to Treg cells; it is also positive in all activated T cells.[3] Therefore, a more specific method is needed.

Targeting a subset of highly suppressive effector Treg cells based on specific molecules uniquely upregulated in response to tumor antigens in the tumor microenvironment is considered a viable option for cancer immunotherapy. Studies have tested the impact of anti-CCR4 antibodies on subsets of human Treg cells in melanoma patients.[3] As a result of this process, it was observed that effector Treg cells expressing CCR4 were selectively eliminated, while pure Treg cells were preserved. Research on this topic is ongoing.

In conclusion, the results obtained from studies suggest that Treg cells in the tumor microenvironment inhibit anti-tumor immunity, posing a significant obstacle to the development of effective treatment methods. Tumor cells not only recruit Treg cells to the tumor site but also induce the transformation of naive or effector T cells into Treg cells through various cytokines mediated by the natural immune system. Particularly, a decrease in the ratio of CD8+ T cells to Treg cells is associated with poor prognosis in various cancer types. To advance cancer immunotherapy, a thorough understanding of Treg cell biology in the context of tumor development and progression is essential. Identifying more specific cell surface markers is a crucial step. The mechanisms through which Treg cells contribute to the establishment of tumor-specific tolerance are becoming an increasingly important focus of research. Understanding Treg cells in depth is necessary to develop new strategies that intervene in the steps leading to Treg cell depletion or the functions they perform. One of the most critical issues in cancer immunotherapy is the autoimmune-related adverse events resulting from the process of targeting Treg cells. This poses a challenging step in cancer treatment.

Declaration of conflicting interests
The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding
The authors received no financial support for the research and/or authorship of this article.

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