



REVIEW PAPER

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Characteristics of Regulatory T cells

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ABSTRACT

Regulatory T cells (Tregs) is heterogenic subpopulation of T cells that is able to suppress function of effector cells during the immune response. Among them are natural (nTreg) and induced Treg (Tr1, Th3, CD4⁺CD25⁻). CD25, CD45Ro, CD152, GITR, LAG-3, several adhesion molecules, chemokine receptors as well as Toll-like receptors are present on the surface of Treg. Mechanism of suppression used by nTreg is not completely understood.

Keywords: Tregs, regulatory T cells, autoimmunity, cancer.

Introduction

The subset of suppressor T cells loomed from the work of Gerdhonn and Kondo in the early 1970s. Although not that widely noted the existence of T cells with suppressive function was also suggested by Nishizuka and Sakakura [1, 2].

This distinct T-cell population was originally characterized in mice, representing 5–10% of peripheral CD4⁺ T cells.

In humans, Treg cell population is a small subset of CD4⁺ T lymphocytes (about 5%), with the expression of high-intensity CD25 (CD25^{high}) and they control immunity by interfering with the generation of effector function *in vivo* [3, 4].

Immunophenotype

Treg population is heterogeneous and markers for specific subtypes are now the major objective.

nTreg lymphocytes were identified as CD4⁺ T cells expressing high levels of IL-2R α (CD25), along with low expression of the IL-7R α chain (CD127) and a unique transcription factor FoxP3, which acts as a master regulator gene for inducing Treg phenotype and lineage [5].

Treg cells express several molecules such as CTLA-4, CD122, GITR, Galectin 10, LAP, ICOS, PD-1 and GARP and Toll-like receptors [6, 7].

Treg cells show elevated levels of adhesion molecules such as CD11a, CD44, CD54, and CD103 [7, 8].

There is some evidence suggesting that Treg cells might also exhibit a characteristic chemokine receptor profile: CXCR3, CXCR4, CCR4, CCR3, CCR5, CCR6 and CCR8 [7, 9, 10].

Others Tregs markers are LAG-3, an MHC class II binding CD4 homologue and neutropilin (Nrp1), which is involved in axon guidance, angiogenesis and T lymphocyte activation [11].

A relatively new marker HELIOS, from the Ikaros family transcription factors, defines Treg subsets with distinct phenotypic and functional characteristics [12].

It has been recently reported that nTregs express CD39 and CD73 antigens. Expression of CD39 and CD73 on Tregs was first described by Borsellino *et al.* and Deaglio *et al.* in 2007 [6, 12].

The FoxP3 gene was identified in 2001 as the disease – causative in Scurfy mice, which spontaneously develop severe autoimmunity/inflammation as a result of a single gene mutation on the X chromosome [11, 13].

FoxP3 seems to activate or repress hundreds of genes directly or indirectly through forming a transcription complex with other key transcription factors such as NFAT [14].

FoxP3 probably controls cell-contact dependent inhibition of the activation and proliferation of T cells,

killing or inactivating APC and/or T cells, and/or via suppression of cytokines such as IL-10 and TGF- β [14–16].

Mechanism of action and role of Tregs

Presently, a role of Tregs is not restricted to maintaining self-tolerance. Tregs are believed to regulate immune response against self-antigens, infectious agents, tumor antigens and transplantation antigens.

Tregs maintain immunological tolerance by inhibiting helper T cell, cytotoxic T lymphocytes, dendritic cells, and NK cells function [17–19].

Tregs can secrete blocking cytokines like IL-10, TGF- β , IL-35 and use them as the main immunosuppression inducing factors [20].

Tregs can also use the cytotoxicity involving perforin and granzyme as a mechanism of suppression. It has been proven that human Tregs activated by anti-CD3 and CD46 express granzyme A and B and can kill their own immune cells. Killing involving Tregs is perforin-dependent and FasL-independent [20].

Tregs may also limit the immune response by affecting the APCs. In studies involving Treg, Tef and DC interactions in lymph nodes using intravital microscopy, it has been shown that Tregs are capable of direct interaction with antigen-binding dendritic cells. Contact between Tregs and DC can lead to Tef activation blocking [20].

Tregs in pregnancy

Tregs induced during pregnancy are involved in immune tolerance induction of mother organism on fetus. On the periphery a double increase in the number of Tregs in pregnancy is observed, and the maximum number of these cells falls on the period from the second trimester and lasts for 6–8 weeks after birth. In women with recurrent, spontaneous miscarriages, the number of Tregs drops suddenly in both decidua as well as in peripheral blood compared with women whose pregnancy is proceeding correctly [21, 22].

Autoimmunity

The Treg function impairment can lead to the development of autoimmune diseases.

In humans, the quantitative and qualitative disorders of Treg populations is said to be one of the courses of this type of diseases [17].

For instance, in both newly diagnosed and chronic type I diabetes patients a reduced percentage of Tregs has been stated. In addition, these cells less inhibited T cell proliferation *in vitro* [23–25].

Treg cells in rheumatoid arthritis patients were in anergy, inhibited the proliferation of effector cells, but did not inhibit the secretion of inflammatory cytokines by effector lymphocytes and monocytes. In patients with multiple sclerosis, there was no decrease of CD4⁺CD25^{high}FoxP3⁺ cells, however the ability to inhibit the effector lymphocyte proliferation, and their cytokine secretion was reduced, compared to the control group [26, 27].

Neoplasms

Numerous studies show connection of T regulatory cells with the induction of tolerance to cancer. Cancer antigens derived from the host and many cancer-associated antigens are also self-antigens, which Treg cells recognize as their own and promote tolerance. Tregs are also capable of inducing suppression of NK cells, which control tumor growth *in vivo*. It has been found that the regulatory T-lymphocytes can induce suppression of both innate and adaptive immune response [28–30].

An increased number of Tregs in the circulation of patients with different types of cancer has been shown (including lung, breast, ovarian, colorectal, esophageal, renal and gastric cancer, as well as hepatocellular carcinomas, leukemias, lymphomas and melanomas). The increased infiltration of Tregs in tumors and neoplastic exudates is associated with poor prognosis in multiple cancers. It is known that infiltration of CD8⁺ cells is a preferred prognostic factor, but increased ratio of Tregs to CD8⁺ cells is a negative factor. It seems that the relationship between Tregs and effector cells in the cancer microenvironment creates the balance between immunity and tolerance. As a result cancer could reduce the immune response by promoting the recruitment, expansion and activation of Tregs [28–32].

Conclusion

Tregs regulatory functions are critically important for maintaining balanced immune responses. In healthy individuals, this balance is controlled by nTregs. In patients with cancer and viral infections, the rules for nTregs are changed. In recent years there has been tremendous progress in understanding the function

of Tregs in cancer, autoimmunity, graft rejection and other reactions depending on immune response. These interdependencies, however, require further clarification.

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Conflict of interest statement

The authors declare no conflict of interest.

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