

制御性 T 細胞を標的とした抗体による悪性腫瘍治療法の開発

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Tumor immunotherapy targeting regulatory T cells

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1. Miyara M, Yoshioka Y, Kitoh A, Shima T, Wing K, Niwa A, Parizot C, Taflin C, Heike T, Valeyre D, Mathian A, Nakahata T, Yamaguchi T, Nomura T, Ono M, Amoura Z, Gorochoy G, Sakaguchi S. (2009)

Functional delineation and differentiation dynamics of human CD4+ T cells expressing the FoxP3 transcription factor.

Immunity, 30: 899-911.

FoxP3 is a key transcription factor for the development and function of natural CD4(+) regulatory T cells (Treg cells). Here we show that human FoxP3(+)CD4(+) T cells were composed of three phenotypically and functionally distinct subpopulations: CD45RA(+)FoxP3(lo) resting Treg cells (rTreg cells) and CD45RA(-)FoxP3(hi) activated Treg cells (aTreg cells), both of which were suppressive in vitro, and cytokine-secreting CD45RA(-)FoxP3(lo) nonsuppressive T cells. The proportion of the three subpopulations differed between cord blood, aged individuals, and patients with immunological diseases. Terminally differentiated aTreg cells rapidly died whereas rTreg cells proliferated and converted into aTreg cells in vitro and in vivo. This was shown by the transfer of rTreg cells into NOD-scid-common gamma-chain-deficient mice and by TCR sequence-based T cell clonotype tracing in peripheral blood in a normal individual. Taken together, the dissection of FoxP3(+) cells into subsets enables one to analyze Treg cell differentiation dynamics and interactions in normal and disease states, and to control immune responses through manipulating particular FoxP3(+) subpopulations.

2. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T, Sakaguchi S. (2008)

CTLA-4 control over Foxp3+ regulatory T cell function.

Science, 322: 271-275.

Naturally occurring Foxp3+CD4+ regulatory T cells (Tregs) are essential for maintaining immunological self-tolerance and immune homeostasis. Here, we show that a specific deficiency of cytotoxic T lymphocyte antigen 4 (CTLA-4) in Tregs results in spontaneous development of systemic lymphoproliferation, fatal T cell-mediated autoimmune disease, and hyperproduction of immunoglobulin E in mice, and it also produces potent tumor immunity. Treg-specific CTLA-4 deficiency impairs in vivo and in vitro suppressive function of Tregs-in particular, Treg-mediated down-regulation of CD80 and CD86 expression on dendritic cells. Thus, natural Tregs may critically require CTLA-4 to suppress immune responses by affecting the potency of antigen-presenting cells to activate other T cells.

3. Yamaguchi T, Hirota K, Nagahama K, Ohkawa K, Takahashi T, Nomura T, Sakaguchi S. (2007)

Control of immune responses by antigen-specific regulatory T cells expressing the folate receptor.

Immunity, 27: 145-159.

Immune responses can be enhanced or dampened by differential manipulation of Foxp3-expressing CD25(+)CD4(+) natural regulatory T (Treg) cells versus other naive or activated T cells. By searching for a molecule capable of distinguishing these populations, we here found that natural Treg cells constitutively expressed high amounts of folate receptor 4 (FR4). The expression of FR4 and CD25 also separated antigen-stimulated CD4(+) non-Treg cells into the FR4(hi)CD25(-) and FR4(lo)CD25(+) populations, which were different in proliferation and cytokine secretion upon restimulation. These distinctions showed that antigenic stimulation activated and expanded antigen-specific natural Treg cells as well as effector and memory T cells. Accordingly, FR4(hi)CD25(+)CD4(+) T cells enriched from alloantigen-stimulated T cells suppressed graft rejection. Administration of FR4 monoclonal antibody specifically reduced Treg cells, provoking effective tumor

immunity in tumor-bearing animals, whereas similar treatment of normal young mice elicited autoimmune disease. Thus, specific manipulation of FR4(hi)CD25(+)CD4(+) Treg cells helps control ongoing immune responses.

4. Shimizu J, Yamazaki S, Sakaguchi S. (2007)

Induction of tumor immunity by removing CD25+CD4+ T cells: a common basis between tumor immunity and autoimmunity.

J Immunol, 163: 5211-5218.

This study shows that removal of a T cell subpopulation can evoke effective tumor immunity in otherwise nonresponding animals. Elimination of CD25-expressing T cells, which constitute 5-10% of peripheral CD4+ T cells in normal naive mice, elicited potent immune responses to syngeneic tumors in vivo and eradicated them. The responses were mediated by tumor-specific CD8+ CTLs and tumor-nonspecific CD4-8- cytotoxic cells akin to NK cells. Furthermore, in vitro culture of CD25+4+ T cell-depleted splenic cell suspensions prepared from tumor-unsensitized normal mice led to spontaneous generation of similar CD4-8- cytotoxic cells capable of killing a broad spectrum of tumors; reconstitution of CD25+4+ T cells inhibited the generation. In this culture, self-reactive CD25-4+ T cells responding to self peptides/class II MHC complexes on APCs spontaneously proliferated upon removal of CD25+4+ T cells, secreting large amounts of IL-2. The IL-2 thus produced appeared to be responsible for the generation of CD4-8- NK cells as lymphokine-activated killer cells, because direct addition of an equivalent amount of IL-2 to the culture of CD4-8- cells generated similar lymphokine-activated killer/NK cells, whereas coculture of normal CD4-8- cells with CD25-4+ T cells from IL-2-deficient mice did not. Thus, removal of immunoregulatory CD25+4+ T cells can abrogate immunological unresponsiveness to syngeneic tumors in vivo and in vitro, leading to spontaneous development of tumor-specific effector cells as well as tumor-nonspecific ones. This novel way of evoking tumor immunity would help to devise effective immunotherapy for cancer in humans.

5. Ko K, Yamazaki S, Nakamura K, Nishioka T, Hirota K, Yamaguchi T, Shimizu J, Nomura T, Chiba T, Sakaguchi S. (2005)

Treatment of advanced tumors with agonistic anti-GITR mAb and its effects on tumor-infiltrating Foxp3+CD25+CD4+ regulatory T cells.

J Exp Med, 202: 885-891.

T cell stimulation via glucocorticoid-induced tumor necrosis factor receptor family-related protein (GITR) can evoke effective tumor immunity. A single administration of agonistic anti-GITR monoclonal antibody (mAb) to tumor-bearing mice intravenously or directly into tumors provoked potent tumor-specific immunity and eradicated established tumors without eliciting overt autoimmune disease. A large number of CD4+ and CD8+ T cells, including interferon (IFN)-gamma-secreting cells, infiltrated regressing tumors. Tumor-specific IFN-gamma-secreting CD4+ and CD8+ T cells also increased in the spleen. The treatment led to tumor rejection in IFN-gamma-intact mice but not IFN-gamma-deficient mice. Furthermore, coadministration of anti-GITR and anti-CTLA-4 mAbs had a synergistic effect, leading to eradication of more advanced tumors. In contrast, coadministration of anti-CD25 and anti-GITR mAbs was less effective than anti-GITR treatment alone, because anti-CD25 depleted both CD25+-activated effector T cells and CD25+CD4+ naturally occurring regulatory T (T reg) cells. Importantly, CD4+ T cells expressing the T reg-specific transcription factor Foxp3 predominantly infiltrated growing tumors in control mice, indicating that tumor-infiltrating natural Foxp3+CD25+CD4+ T reg cells may hamper the development of effective tumor immunity. Taken together, T cell stimulation through GITR attenuates T reg-mediated suppression or enhances tumor-killing by CD4+ and CD8+ effector T cells, including those secreting IFN-gamma, or both. Agonistic anti-GITR mAb is therefore instrumental in treating advanced cancers.