

Regulatory T cells in anti-tumor immune response

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Abstract

Naturally occurring CD4⁺ CD25⁺ regulatory T cells originally proposed by Sakaguchi *et al.* play an important role in maintaining immunological balance in hosts by suppressing a wide variety of immune responses. We have recently proposed that a category of serologically-defined self-antigens by SEREX methodology constitute antigens recognized by both CD4⁺ CD25⁺ naturally occurring regulatory T cells and CD4⁺ helper T cells. Immunization of mice with plasmids encoding immunogenic self-antigens, but not heterologous antigens resulted in enhancement of pulmonary metastasis following i.v. challenge with syngeneic tumor cells and acceleration of tumor development induced by methylcholanthrene. Detailed analysis showed that metastasis enhancement and acceleration of tumor development were due to the immunosuppressive effects of CD4⁺ CD25⁺ T cells in the immunized hosts. These CD4⁺ CD25⁺ T cells suppressed the activity of invariant NKT cells and NK cells. In addition, the CD4⁺ CD25⁺ T cells strongly suppressed *in vitro* peptide-specific proliferation of CD4⁺ CD25⁻ T cells and CD8⁺ T cells, indicating their broad suppressive activity in a wide range of immune responses. In contrast, coimmunization with a mixture of plasmids encoding a tumor-specific CTL epitope and these SEREX-defined self-antigens or heterologous antigens led to a marked increase in the number of peptide-specific CD8⁺ CTL and to heightened resistance to challenge with syngeneic tumors expressing the CTL epitope. This heightened helper response was dependent on CD4⁺ T cells and on co-presentation of the CTL epitope with the SEREX-defined self-antigens.

These results indicate that immunization with SEREX-defined self-antigens leads to generation/activation of either CD4⁺ CD25⁺ regulatory T cells with potent suppressive activity or CD4⁺ CD25⁻ helper T cells essential for amplification of CD8⁺ CTL. IFN- γ produced by peptide-specific CD8⁺ T cells is essential to control the generation/activation of CD4⁺ CD25⁺ regulatory T cells.

Glucocorticoid-induced TNF receptor family-related gene (GITR) is reported to possess direct functional relevance with regard to naturally occurring regulatory T cells as indicated by evidence that agonistic anti-GITR antibody blocks the suppressive activity of regulatory T cells. It has also been shown that the reversal of suppression by anti-GITR antibody is attributable to the costimulatory activity of anti-GITR antibody on the responder CD4⁺ CD25⁻ T cells. Treatment of tumor bearing hosts with agonistic anti-GITR antibody resulted in tumor suppression while treatment with anti-CD25 antibody failed to do so.

Recently, regulatory T cells with CD8⁺ CD122⁺ phenotype was proposed by Suzuki *et al.* This T cell subset may also possess some role in controlling anti-tumor immune responses.