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## Regulatory T cells in anti-tumor immune responses

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### Abstract

Anti-tumor immune response is a complexity of cellular and molecular interactions among a variety of immunocompetent cells. CD8+ CTL represent major effector cells with a capacity of direct tumor destruction. Recently reported NKT cells may also be effector cells in more innate type immune responses. They possess TCR of extremely limited variations with a use of V $\alpha$ 14-J $\alpha$ 281 in murine TCR genes and of V $\alpha$ 24-J $\alpha$ 15 in human TCR genes. Their TCR bind CD1d with non-natural glycolipids, alpha-galactosylceramide (alpha-Galcer) which are absent in mammalian host.

While CD4+ T cells do not directly destroy tumor target cells in general, they may play essential roles in regulating anti-tumor immune responses in multiple mechanisms. CD4+ helper T cells recognizing cognate tumor antigen peptides presented by MHC class II molecules may amplify activation and clonal expansion of CTL. Regulatory T cells with CD4+, CD25+ phenotypes are also of considerable interest. They were demonstrated in their suppressive effects on development of a variety of autoimmune diseases, and more recently of anti-tumor immune responses. Though most of these regulatory T cells are supposed to recognize self-antigen peptides, molecular profiles of antigens are still unknown. Despite growing recognition of their importance, antigenic and functional relationship between helper T cells and regulatory T cells remain elusive.

We have recently reported that immunogenic wild type molecules derived from chemically induced murine sarcomas, strongly enhance activity of CD8+ CTL specific for a tumor rejection antigen. These immunogenic molecules were identified by an expression cloning method, SEREX, with the use of IgG class antibodies present in sera of tumor bearing hosts. Coimmunization of mice with a mixture of plasmids encoding CTL antigens and SEREX-defined antigens in the presence of host CD4+ T cells drastically enhanced the number of tumor specific CD8+ CTL, and also *in vivo* tumor rejecting activities, which suggest these antigens being recognized by CD4+ helper T cells involved in anti-tumor immune responses.

On the contrary, immunization of hosts with plasmids encoding these SEREX-defined antigens alone resulted in remarkable enhancement of *in vivo* tumor growth presenting aggravated pulmonary metastasis. CD4+ CD25+ T cells of hosts immunized by SEREX-defined wild-type antigens are responsible for metastasis enhancement by regulating NKT cells in pulmonary compartments.

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