

Regulatory T cells recognizing SEREX-defined selfantigens in anti-tumor immune response

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Evidence for the essential role of regulatory T cells in maintaining immunological homeostasis comes from a range of *in vitro* and *in vivo* experimental systems, and naturally occurring regulatory T cells co-expressing CD4 and CD25 are of central interest with regard to the regulation of autoreactive T cells. A number of selfantigens are considered natural ligands for the maintenance of regulatory T cells while their molecular profiles are still elusive.

We have recently reported that immunization with serologically-defined broadly expressed selfantigens results in enhancement of pulmonary metastasis of *i.v.* challenged syngeneic transplantable tumor lines. These selfantigens were identified by serological identification of antigens by recombinant expression cloning (SEREX), a methodology widely used to identify immunogenic molecules in mice and human tumors. CD4⁺ CD25⁺ T cells obtained from mice immunized with SEREX-defined selfantigens had strong suppressive activity on peptide-specific proliferation of CD4⁺ CD25⁻ T cells and CD8⁺ T cells. The suppressive effect was observed without *in vitro* T-cell stimulation. *Foxp3* expression in these CD4⁺ CD25⁺ T cells from immunized mice was five to ten times greater than CD4⁺ CD25⁺ T cells derived from naive mice. Their *in vitro* suppressive activity essentially disappeared eight weeks after the last immunization. However, it was regained by *in vitro* restimulation with cognate selfantigen (Dna J-like 2) protein but not with control protein. We propose that SEREX-defined selfantigens such as those used in this study represent selfantigens that elicit naturally occurring CD4⁺ CD25⁺ regulatory T cells.

We also examined the role of CD4⁺ CD25⁺ regulatory T cells in the development of 3-methylcholanthrene (MCA)-induced tumors. Immunization of wild-type BALB/c mice with a series of SEREX-defined selfantigens resulted in acceleration of tumor development. Acceleration of tumorigenesis was also observed in mice adoptively transferred 2 or 4 weeks after MCA injection with CD4⁺ CD25⁺ T cells derived from mice immunized with Dna J-like 2, one of these selfantigens. Experiments with *J(alpha)281^{-/-}* mice lacking NKT cells indicated that NKT cells responsible for regulating the development of MCA-induced tumors were suppressed in immunized hosts. We propose that CD4⁺ CD25⁺ regulatory T cells generated by immunization with these selfantigens enhance susceptibility to MCA induced-tumorigenesis by controlling NKT reactivity, and suggest that these observations are the strong evidence for the existence of cancer immunosurveillance in this system of chemical carcinogenesis.

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