

# Natural CD4<sup>+</sup> regulatory T cells in tumor immunity

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There is accumulating evidence that naturally arising CD4<sup>+</sup> regulatory T cells (TR cells), the majority of which constitutively express CD25, actively contribute to the maintenance of natural immunologic self-tolerance. Self-tolerance maintained by natural CD25<sup>+</sup>CD4<sup>+</sup> TR cells may, however, impede development of tumor immunity by hampering the generation and activation of tumor-effector T cells recognizing autologous tumor cells. If this is the case, reduction of CD25<sup>+</sup>CD4<sup>+</sup> TR cells or attenuation of their suppressive activity may enhance immune responses to autologous tumor cells.

We have examined whether the treatment of tumor-bearing mice with monoclonal antibodies (mAbs) specific for the molecules expressed by natural TR cells (e.g., CD25, CTLA-4, and GITR) can provoke or enhance tumor immunity through reduction of their number or suppressive activity. For example, administration of anti-GITR mAb (DTA-1), especially in combination with anti-CTLA-4 mAb, enhanced tumor immunity, leading to eradication of established tumors. Both mAbs not only abrogated *in vitro* TR cell-mediated suppression but also enhanced the activity of effector T cells in a synergistic manner. Manipulation of GITR-ligand can also enhance tumor immunity by a similar mechanism. In addition, our newly raised mAb that can differentiate natural TR cells from activated T cells in general provoked effective tumor immunity when administered to tumor-bearing animals.

In monitoring natural TR cells in the local tumor environment, the most specific molecular marker for TR cells at the moment is *Foxp3*, which is a forkhead/winged-helix transcription factor. *Foxp3* is specifically expressed by CD25<sup>+</sup>CD4<sup>+</sup> TR cells and appears to be a master control gene for their development and function. We show that monitoring of *Foxp3*<sup>+</sup> T cells in tumor infiltrating T cells can be instrumental for assessing local tumor immunity.

## References

1. Sakaguchi S. Naturally arising CD4<sup>+</sup> regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol* 2004; **22**: 531-62. (PMID: 15032588) [PubMed]
2. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor *Foxp3*. *Science* 2003; **299**: 1057-61. (PMID: 12522256) [PubMed]
3. Shimizu J, Yamazaki S, Takahashi T, Ishida Y, Sakaguchi S. Stimulation of CD25<sup>+</sup>CD4<sup>+</sup> regulatory T cells through GITR breaks immunological self-tolerance. *Nat Immunol* 2002; **3**: 135-42. (PMID: 11812990) [PubMed]
4. Takahashi T, Tagami T, Yamazaki S, Uede T, Shimizu J, Sakaguchi N, Mak TW, Sakaguchi S. Dominant immunologic self-tolerance maintained by CD25<sup>+</sup>CD4<sup>+</sup> regulatory T cells constitutively expressing CTLA-4. *J Exp Med* 2000; **192**: 303-10. (PMID: 10899917) [PubMed]
5. Shimizu J, Yamazaki S, Sakaguchi S. Induction of tumor immunity by removing CD25<sup>+</sup>CD4<sup>+</sup> T cells: a common basis between tumor immunity and autoimmunity. *J Immunol* 1999; **163**: 5211-8. (PMID: 10553041) [PubMed]
6. Onizuka S, Tawara I, Shimizu J, Sakaguchi S, Fujita T, Nakayama E. Tumor rejection by *in vitro* administration of anti-CD25 (Interleukin-2 receptor alpha) monoclonal antibody. *Cancer Res* 1999; **59**: 3128-33. (PMID: 10397255) [PubMed]

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