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Naturally arising CD25+ CD4+ regulatory T cells in auto-immunity and tumor immunity

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Abstract

There is accumulating evidence that naturally arising CD4+ regulatory T cells (T-reg), the majority of which constitutively express CD25, actively contribute to the maintenance of natural immunologic self-tolerance. Removal of CD25+ CD4+ T-reg from the periphery of normal mice, for example, leads to spontaneous development of various autoimmune diseases. CD25+ CD4+ T-reg also constitutively express CTLA-4 and GITR (glucocorticoid-induced TNF receptor-related gene); and blockade of CTLA-4 or ligation of GITR on the T-reg by specific monoclonal antibodies (mAbs) can attenuate their suppressive activity, leading to the development of autoimmune disease.

As the other side of the coin, naturally present CD25+ CD4+ T-reg may impede development of tumor immunity by hampering the generation and activation of tumor-effector T cells recognizing autologous tumor cells. Indeed, reduction of CD25+ CD4+ T-reg by administration of anti-CD25 mAb for a limited period provoked effective tumor-specific immunity against syngeneic tumor cells. Furthermore, administration of anti-CTLA-4 or anti-GITR mAb resulted in enhanced tumor immunity partly due to attenuation of the suppressive activity of natural CD25+ CD4+ T-reg and consequent activation of tumor effector cells. Tumor effector cells can also be generated *in vitro* by simply eliminating CD25+ CD4+ T cells from splenic cell suspensions prepared even from tumor-nonsensitized mice. In this *in vitro* induction of tumor immunity, CD25- CD4+ T cells responding to self-peptides/class II MHC molecules expressed on syngeneic APCs spontaneously proliferated upon removal of CD25+ CD4+ regulatory T cells. A large amount of IL-2 produced by such CD4+ self-reactive T cells generated NK-like tumor effector cells as lymphokine-activated killer (LAK) cells capable of promiscuously killing various tumor cells.

Thus, removal or functional alteration of CD25+ CD4+ T-reg 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.

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