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Regulatory T cells and GVHD

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Keywords

GVHD, phenotype, regulatory T cells

Context

So-called 'suppressor' or 'regulatory' T cells are thought to prevent activation, in the periphery, of two cell types: antigen-presenting cells (APCs) that present endogenously processed self-antigens, and self-reactive T cells that have escaped thymic deletion (see Additional information [1]). It was found that T cells with the phenotype $CD4^+CD25^+$ can prevent autoimmune disease in the context of neonatal thymectomy when adoptively transferred (see Additional information [2]). This paper investigated whether T cells of the same phenotype could transfer tolerance for alloantigen in both *in vitro* and *in vivo*allogeneic T-cell transfer models of graft-versus-host disease (GVHD).

Significant findings

T-cell proliferation occurred *in vitro* when APCs were incubated with allogeneic T cells in a mixed lymphocyte reaction (MLR). When CD40L was blocked, tolerance to the alloantigen occurred. When the T cells were restimulated with the same APCs in a secondary MLR, proliferation was suppressed. Depletion of $CD4^+CD25^+$ T cells prior to the primary MLR abrogated the induction of hyporesponsiveness to alloantigen rechallenge in the secondary MLR after anti-CD40L costimulatory blockade in the primary allogeneic MLR. Moreover, purified $CD4^+CD25^+$T cells in high concentrations suppressed a primary MLR.

In vivo, mice inoculated with T cells from an MLR cultured without blocking antibody all died from GVHD, whereas adoptive transfer of T cells cultured in allogeneic MLR in the presence of either anti-B7 or anti-CD40L monoclonal antibody did not induce GVHD. In a similar fashion to the *in vitro* experiments, depletion of $CD4^+CD25^+$ T cells from MLR before transfer abrogated protection against GVHD.

Comments

These data demonstrate that $CD4^+CD25^+$ T cells regulate other T cells *in vitro* and *in vivo*. The studies are consistent with a large body of literature demonstrating the regulatory capacity of this T cell subset, and broaden the concept of their capacity for regulation, to alloantigen. As both $CD4^+CD25^+$ and $CD25^-$ T cells expressed CD40L, the data suggest (surprisingly) that blockade of CD40 or B7 costimulation has no effect on effector function of $CD4^+CD25^-$ T cells, but that inhibition of either of these pathways can induce the $CD4^+CD25^+$regulatory subset.

Although intriguing, the *in vivo* model studied is a very limited one, essentially carrying out an MLR in an animal. It will be of physiological relevance to determine whether tolerance induced *in vivo*with anti-CD40L or anti-B7 (in grafting and autoimmune models) is mediated by similar mechanisms. For example, could these antibodies block autoimmune diseases in neonatal thymectomy models? From a clinical perspective, a testable hypothesis is that the more the autoimmune disease patient is CD4-deficient (depleted of regulatory T cells), the harder it is to induce remission/tolerance - a concept with implications for stem cell grafting in autoimmune disease.

Methods

Adoptive transfer, MLR

Additional information

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