PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

CD25^{+} CD4^{+}immunoregulatory T cells

ArticleInfo		
ArticleID	:	204
ArticleDOI	:	10.1186/ar-2000-66784
ArticleCitationID	:	66784
ArticleSequenceNumber	:	161
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2000–2–21 OnlineDate : 2000–2–21
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	130753311

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Keywords

CD4 T cells, CD25, immunoregulatory T cells, tumor immunity

Context

Although this paper does not deal specifically with arthritis, its relevance lies in the intriguing speculations it raises on the common basis for autoimmunity and tumor immunity. It suggests that a regulatory T cell controls both tumor specific and self-reactive T cells. Studies show that a subpopulation of $CD4^+$ T cells prevents autoimmune disease in a number of rodent models. Many studies have previously suggested this regulatory T cell population is $CD25^+$ $CD4^+$, and is anergic (non-proliferative) in normal mice. Stimulation of the regulatory T cells suppresses the activation/ proliferation of other $CD4^+$ or $CD8^+$ T cells in an antigen non-specific manner. Removal of $CD25^+$ $CD4^+$ T cells elicits autoimmunity, and enhances immune responses to non-self antigens such as allogeneic tissue grafts. Here the authors investigate the hypothesis that removal of $CD25^+$ $CD4^+$ immunoregulatory T cells may evoke immune responses to autologous tumor cells by allowing activation of anti-tumor effector cells. To investigate the role of immunoregulatory $CD25^+$ $CD4^+$T cells in tumor immunity.

Significant findings

Balb/c nu/nu mice were simultaneously given a Balb/c spleen suspension depleted of $CD25^+$ cells (CD25-depleted) and RL1 tumor cells (subcutaneous transplant). Transfer of CD25-depleted cells allowed prolonged survival. Upon rechallenge with a larger RL1 dose, mice receiving CD25-depleted cells rejected tumor cells more rapidly. *In vitro*, CD25-depleted spleen suspensions (from tumor unsensitised mice) cultured with or without RL1, showed significant, promiscuous killing activity against both autologous, natural killer (NK)-resistant and allogeneic tumor cells. Two types of cytotoxic cells were isolated from protected mice: $CD8^+$ CTLs, which killed autologous (RL1) tumor, and $CD4^-$ $CD8^-$ T cell receptor $^-$ NK1.1, which were responsible for the promiscuous killing activity. *In vitro*, generation of NK cytotoxic cells was dependent on a population of $CD4^+$ $CD25^-$ T cells. Blocking

studies indicate these $CD4^+$ T cells required self peptide/MHC class II complexes on antigen presenting cells. Exogenous IL-2 substituted for the effect of $CD4^+$ T cells in generating CTLs. Mice which received CD25-depleted cell transfers rejected transplants, but developed autoimmune diseases including gastritis, thyroiditis and oophoritis. If $CD4^+$ cells were eliminated from the CD25-depleted cell transfers, the mice did not develop autoimmune disease. Transfer of $CD8^+$or NK CTLs alone did not result in autoimmunity.

Comments

This interesting paper presents evidence for the delicate balance between effective tumor immunity and autoimmune disease (such as gastritis, thyroiditis and oophoritis). A number of studies demonstrate that many tumor antigens are normal self-constituents, and are recognised by autologous cytotoxic T lymphocytes (CTLs). Moreover, cancer immunotherapy, by vaccination with tumor antigens or transfusion of CTLs, frequently elicits autoimmunity as a result of cross-reactions between tumor antigens and normal tissue antigens. Such findings suggest that autoimmunity is integral to tumor immunity. The authors thus speculate that breaking immunological self-tolerance (by removal of immunoregulatory $CD25^+$ $CD4^+$ T cells) may evoke effective tumor immunity in otherwise non-responding individuals, but risk onset of autoimmune disease.

Methods

Mice used were Balb/c, Balb/c-nu/nu, C57BL/6 (B6) C3H/HE and B6-beige (bg/bg). A number of studies used interleukin (IL)-2, IL-4 or interferon (IFN)-? gene knockout mice. Tumor cells were RL1 (Balb/c-derived radiation leukemia), B16 (B6-derived melanoma), X5563 (C3H-derived plasmacytoma) and P815 (DBA/2-derived mastocytoma). T cell subpopulations, prepared from spleen, were cultured *in vitro*with or without mitomycin C-treated tumor cells, and were subsequently tested for cytotoxicity in a chromium release assay, or for proliferation and IL-2 production. Autoimmune disease was assessed by histological or serological tests for gastritis and thyroiditis.

References

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