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

New Treg and its mechanism of suppression

ArticleInfo		
ArticleID	:	148
ArticleDOI	:	10.1186/ar-2000-66848
ArticleCitationID	:	66848
ArticleSequenceNumber	:	105
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–9–26 OnlineDate : 2000–9–26
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	130753311

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Keywords

Antigen presentation, Fas, tolerance

Context

Evidence is accumulating regarding the existence and mechanism of suppression of regulatory T cells in the fields of both autoimmunity and transplantation. Interest is growing in the possibility that such T cells could be expanded and harnessed to antigen-specific tolerance for treatment or prevention of autoimmunity and transplant rejection. A previous set of investigations showed that naive $CD8^+$ ovalbumin (OVA)-specific TCR-transgenic T cells underwent slow deletion by a Fas-dependent mechanism after adoptive transfer into transgenic mice expressing OVA in the pancreas (RIP-mOVA mice). This occurred in lymph nodes draining the pancreas, and was presumed to result from migration of tolerogenic dendritic cells bearing OVA, from pancreas to draining lymph nodes (see Additional information [1-3]). Despite careful searching, the antigen presenting cell (APC) has not been found.

Significant findings

The T cells were mature transgenic-TCR^+ $CD4^-$ $CD8^-$ (antigen-specific double-negative, DN). When cloned, they grew in the presence of IL-2, IL-4 and L^{d+} APCs, and suppressed proliferation and function of transgenic-TCR^+CD8^+ T cells. They could be purified from spleens of lymphocyte-treated and naive mice.

The phenotype of the clone was $NK1.1^-$ $CD28^-$ $CD44^-$ $CD30^+$. The mechanism of suppression was shown to require cell contact between DN and $CD8^+$ T cells. The DN cells were found to kill TCR^+ $CD8^+$ T cells in a Fas-dependent manner. This could occur through acquisition of the presenting molecule, Ld, by the DN T cells from other APC, turning DN T cells into 'killer APC'.

Comments

The paper identifies a novel subset of DN regulatory T cells, likely to be present in normal lymphoid organs but which expand on exposure to antigen (donor-specific T cell infusion). This paper raises the fascinating possibility that these DN T cells can acquire MHC class I/peptide from local or migratory APCs, for generation of 'killer APC'. It will be interesting to see whether sucha mechanism can also be invoked for self-reactive $CD4^+$ T cells, as T cells are also able to acquire MHC class II/self peptide complexes (see Additional information [4]).

Regulatory DN T cells are distinct from so-called Tr1 cells that can be induced *in vitro* by repetitive presentaion of antigen in the presence of IL-10. $CD4^+$ Tr1 clones demonstrate a differentiated memory T cell phenotype, proliferate poorly, secrete IL-10, but little IL-2 or IL-4, and , when antigen-activated inhibit development of clitis iduced in SCID mice by transfer of $CD45RB^{bright}$ $CD4^+$ T cells (see Additional information [5]). This suppression is dependent on IL-10 and TGF?.

Methods

adoptive transfer, TCR transgenic mice, MLR (mixed lymphocyte response)

Additional information

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