Induction of IgE synthesis by genetically modified CD8+ T cells of a patient with adenosine deaminase deficiency

http://www.firstlight.cn 2006-03-16

We have previously reported that an adenosine deaminase (ADA)-deficient patient treated with T cell-directed gene therapy had an increase in serum IgE levels, despite a marked inversion of the CD4/CD8 ratio. In the present report, we have analyzed the phenotypic and functional profiles of the patient's lymphocytes obtained during the clinical trial. In peripheral blood mononuclear cells (PBMC) that were freshly prepared from the patient, both CD4+ and CD8+ T cell subsets were negative for CD40 ligand (CD40L; CD154) and Fas ligand (FasL; CD95L), while CD20+ B cells constitutively expressed CD40 and HLA-DR and were negative for CD80, CD86 and Fas (CD95). The expression of CD23 was detected on the majority of CD20+ B cells and expression was upregulated by interleukin (IL)-4. Furthermore, the patient's PBMC, which already expressed both germline and mature Cεtranscripts in vivo, spontaneously secreted IgE and responded to IL-4 with increased IgE production during in vitro culture. When stimulated with anti-CD3ε monoclonal antibody (mAb), CD8+ T cells from gene-transduced T cells displayed high production of interferon (IFN)-γ, low production of IL-4 and IL-13 and comparable levels of CD40L and FasL expression; however, lined CD8+ T cells from circulating T cells expressing the transgene produced IL-4 and IL-13 together with smaller amounts of IFN-γ and preferably expressed CD40L rather than FasL. Two such CD8+ T cells, in conjunction with the presence of IL-4, supported CD40L- mediated B cell proliferation and IgE production after stimulation and fixation. These results indicate that ADA-deficient B cells are functionally mature and that gene-transduced CD8+ T cells and lined CD8+ T cells containing the transgene exhibit T helper 0- and T cytotoxic (c) 2-like phenotypes, respectively. Our data also suggest that immuno-logic reconstitution with genetically modified CD8+ T cells may promote IgE production.

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