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Targeted arthritis gene therapy with T cells

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David Gould,[Aff1]

Aff1 Queen Mary, University of London, UK

Keywords

Arthritis, gene therapy, IL-12 p40, T cells

Context

CD4$^+$ T cells have tissue-specific homing properties and are observed in target organs in autoimmunity. As such, these cells could be utilised as carrier cells to achieve local expression of immunoregulatory genes at disease sites. IL-12 is a heterodimeric cytokine that promotes Th1 differentiation of T cells. The p40 subunit of IL-12 expressed by itself, however, is an antagonist of IL-12 function and therefore has potential therapeutic benefit in arthritis. To provide direct evidence of T cell homing to disease sites in the mouse collagen-induced arthritis (CIA) model, the authors have utilised collagen type II (CII)-specific primary T cells and hybridomas derived from CII-specific TCR transgenic mice. Cells engineered to express reporter genes enabled analysis of *in vivo* localisation, and cells transduced to express IL-12 p40 were assessed for therapeutic effect.

Significant findings

Adoptively transferred CII-specific T-cell hybridomas localised to, and remained within, both asymptomatic and arthritic joints in CIA, whilst localisation in the joints of naive animals was only transient. Hybridomas with antigen specificity for myelin basic protein (MBP) also localised to normal and diseased joints but only transiently. When CII-specific hybridomas were engineered to express IL-12 p40 they inhibited disease development when delivered before disease onset, whilst MBP-specific hybridomas expressing IL-12 p40 were not effective. Hybridomas with dual antigenic specificities modulated cytokine balance (IFN?, IL-4) in draining lymph nodes but did not alter T-cell proliferation or systemic antibody production. Therefore, the therapeutic effect observed with CII-specific cells was postulated to be due to their unique ability to localise to and express IL-12 p40 within joints. In addition, primary CD4$^+$ lymphocytes isolated from CII transgenic mice were also therapeutic when transduced to express IL-12 p40.

Comments

There are some interesting aspects to this study, particularly the demonstration that CII-specific T-cell hybridomas selectively localise to, and are retained within, the joints of CII immunised and arthritic animals. The postulation that CII-specific T cells exert therapeutic effects locally within the joint is in agreement with an earlier report by another group (see Additional information [1]), which utilised a similar experimental model for transfer of antigen specific T cells. These observations may indicate that local expression of IL-12 p40 within joints alters the environment to Th1 with therapeutic effect and may point the way to potentially selective therapeutic approaches for arthritis. As CII-specific T cells were shown to localise in arthritic joints it would be of great interest to examine the therapeutic effect of IL-12 p40 transduced cells when delivered during established disease. One omission from the paper was reference to the first studies using lymphocytes to deliver therapeutic genes in experimental (see Additional information [2,3]).

Methods

Hybridoma synthesis, retroviral transduction, whole-body bioluminescence, cell culture, CIA, ELISA, FACS, RT-PCR

Additional information

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