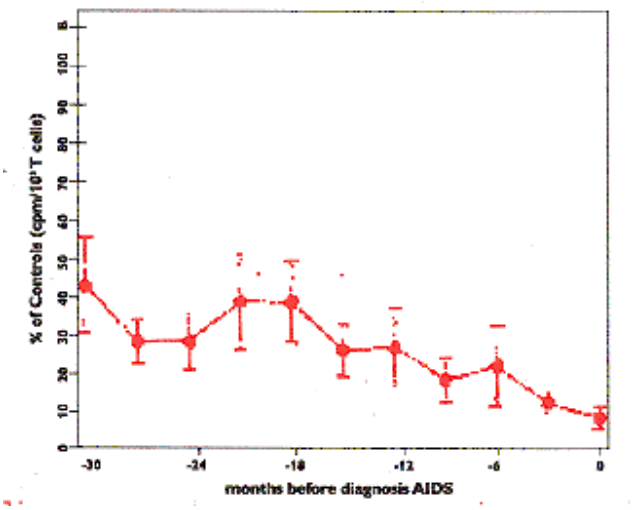
Background

A simple test for cellular immunocompetence

Before monoclonal antibodies became available, polyclonal stimulation of T lymphocytes by lectins (e.g. phytohemagglutinin, PHA and concanavalin A), ConA was commonly used to investigate T cell reactivity in patients, e.g. in the diagnosis of (cellular) immunodeficiency. However, in the last decade lectin stimulation has become obsolete, since more relevant information is obtained by using stimulation by McAbs. CD3 is a T cell-specific determinant, comprised of a group of five polypeptides that are in close association with the two peptide chains of the T cell antigen receptor. The CD3-chains are involved in signal transduction to the cell nucleus and thereby initiate stimulation and division of the T cell. It has been demonstrated that anti-CD3 antibodies alone are insufficient to induce T cell proliferation. A second signal is needed, e.g. in the form of an antigen-presenting cell or a co-stimulatory antibody such as anti-CD28. However, when cross-linked, e.g. by binding to a solid surface such as a tissue culture well, an anti CD3 McAb can directly stimulate T cells to proliferation[1]. Furthermore, it has been found that CD3 McAbs of the IgE isotype are able to stimulate T cells directly, without the need for a second signal[2].

At Sanquin (formerly CLB), a whole-blood lymphocyte culture system[3] has been developed as a simple, reliable and fast method to test for T cell reactivity in patients, in which anti CD3 McAb of the IgE class is used as the stimulant. This IgE anti CD3 antibody was developed at the CLB as a switch variant originating from an IgG1 anti CD3 McAb. As an example of a diagnostic application, we show here data obtained in a group of HIV-infected individuals, in which was studied to what extent progression towards AIDS could be predicted by testing the cellular immunocompetence[4]. Indeed, responses to anti-CD3 were already absent when other markers, e.g. CD4+ T cell numbers, were still normal. In a disease-free survival analysis, low anti-CD3 reactivity predicts progression to AIDS[4].



T cell reactivity induced by CD3 McAb. Ordinate: mean counts/minute ^{3}H-thymidine incorporation per 10^5 T cells in a group of 122 HIV-infected men, as a percentage of the reactivity of 3 healthy control subjects. Abscissa: months prior to the diagnosis of AIDS at t=0.

CD2, CD3, CD28 and T cell stimulation

In general, two signals are required to activate T lymphocytes into proliferation. *In vivo*, such two signals are e.g. stimulation by antigen and binding of a ligand (which can be presented by e.g. an anti-processing cell) to a counter-structure on the T cell membrane. *In vitro*, both signals can be given by the proper combination of monoclonal antibodies. In this respect, monoclonal antibodies against CD2, CD3 and CD28 have provided much information on the stimulatory mechanism. The T lymphocyte membrane determinant CD2 was initially known as the SRBC- or E-receptor for sheep and red blood cells. Indeed, in ‘pre-monoclonal days’ rosette formation with SRBC was the

only method to enumerate and separate human T lymphocytes. Later, monoclonal antibodies emerged and the SRBC-binding structure became known as the CD2 molecule. Subsequently, it was found that anti-CD2 antibodies are also able to stimulate T cells, although only in the presence of a second signal, which can be given either by a second anti-CD2 antibody directed against another epitope on the CD2 molecule, or e.g. by an anti-CD28 antibody. CD28 is a molecule expressed on 95% of CD4+ helper T cells and about half of the CD8+ (cytotoxic) T cells. The binding of anti-CD28 McAbs to T cells was found to enhance stimulation of the cells by anti-CD2 and anti-CD3 McAbs. Therefore, CD28 is regarded as a 'co-stimulatory' molecule[5].

References:

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