Use of Antibodies as Carriers for T-Cell Epitopes

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T cells recognize proteolytic fragments of proteins (= immunogenic peptides or T-cell epitopes) presented on HLA molecules. Presentation of peptides of exogenous proteins normally occurs on HLA class II structures, while epitopes of endogenous or viral proteins are presented on HLA class I molecules. The type of antigen presenting cell is also of importance for the immune response evolving, since presentation by dendritic cells is capable to trigger a proliferative and cytotoxic immune response [1], while presentation by macrophages favors a proliferative response. In the context of allergic reactions, it is specifically interesting that peptide presentation on aberrantly HLA-DR expressing cells (i.e. thyrocytes in Hashimoto thyroiditis or keratinocytes after interferon treatment) is able to induce clonal anergy, which would be an interesting approach to stop allergic reactions. An insufficient interaction with accessory cell molecules is probably responsible for this failure of a proliferative response [2]. To further evaluate the importance of the type of the antigen presenting cell, we established a system which allows to select the antigen presenting cell.

Tetanus toxoid (TT) or an HLA class II binding peptide of TT (residue 830–843, P2) was covalently coupled to anti-CD4, anti-CD8 or anti-CD2 monoclonal antibodies. T cells themselves were chosen as potential antigen presenting cells, as they express HLA-DR after activation and are able to process and present antigens [3], but are unable to capture the antigen. T-cell lines or clones were incubated with these constructs, the proliferative response of TT or P2-specific T-cell clones was evaluated.

6,000
8,000
10,000
0 2,000 4,000
 ^3H -thymidine uptake, cpm

Fig. 1. P2-specific T-cell clones were incubated with the indicated reagents and the proliferation measured after 48 h. P2 alone was stimulatory, since this peptide directly binds to the HLA-DR structures and does not require further processing. TT was not stimulatory, since the T cells were unable to capture this protein antigen. However, TT coupled to anti-CD4 or CD2 antibodies was stimulatory.

While TT itself was not stimulatory for P2-specific CD4⁺ T-cell clones in the absence of accessory cells, addition of TT coupled to anti-CD4 or CD2 antibodies was able to elicit a proliferative response. The peptide P2 itself also stimulated the P2-specific clones, as this peptide was presented by HLA class II expressing T cells without need of processing (fig. 1.)

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CD4/P2 or CD2/P2 constructs were – on a molar basis – 100–500 times more immunogenic as the soluble peptide. T-cell stimulation via antibody/peptide constructs involved intracellular processing, as PPD-specific, irradiated or glutaraldehyde-fixed T-cell lines pulsed with the antibody/TT or antibody/peptide construct could present the peptide and stimulate peptide-specific T-cell clones and protease inhibitors like leupeptin could inhibit the proliferative response to the antibody/peptide construct but not to the peptide alone (data not shown). In contrast to antigen presentation by keratinocytes or thyrocytes etc., antigen presentation by HLA class II expressing T cells did not induce clonal anergy to this specific antigen, since antibody/peptide or antibody/TT pulsed T cells could induce a proliferative response of resting TT-specific memory T cells.

Our data show that (a) antibody/peptide constructs are suitable to direct a certain epitope to a cell; thereby we could make activated T cells to antigen presenting cells for a protein which they normally do not present; (b) compared to peptide alone, antibody/peptide constructs were 100–500 times more immunogenic; (c) peptide presentation on HLA class II expressing T cells is sufficient to elicit a proliferative response of activated and also resting T cells.

References

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