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Antibody-based immunoreceptors: the impact of signalling domain, binding affinity and costimulation

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The immunoreceptor strategy is based on grafting of T cells with recombinant T cell receptor molecules that consist extracellularily of a scFv domain for MHC-independent antigen binding and intracellularily of the CD3 ζ- or FcεRI γ-signalling domain for cellular activation. Upon binding to antigen-positive cells, grafted T cells are activated, secrete IFN-γ, and lyse specifically antigen-positive, but not antigen-negative target cells. During the last years, we generated a panel of immunoreceptors with specficity for "tumor associated antigens" as targets for use in adoptive immunotherapy of malignant diseases: CEA, CA72-4, CA19-9 for gastrointestinal carcinomas, CD30 for Hodgkin's lymphoma and cutaneous T cell lymphoma, HMW-MAA and melanotransferrin for melanoma, and ErbB2 for a variety of carcinomas [1,2]. T cells taken from the peripheral blood of tumor patients and grafted with the appropriate immunoreceptor mediate a highly efficient immune response towards autologous, antigen expressing target cells *in vitro* [3].

One of the major advantages of the immunoreceptor strategy lies in the modular compositon of the receptor molecule. However, little is known about the impact of the individual receptor modules on cellular activation in a complex immunological context. We have identified several items that affect the efficacy of receptor mediated cellular activation including: the signalling domain that affects the stability of immunoreceptor expression and function in T cells [4]; the affinity of the scFv domain that affects the efficacy of T cell activation; B7-1 and B7-2 costimulation that affects the quality of T cell activation [5-7].

The high complexity of the recognition and signalling process makes it unlikely that a universal configuration of the immunoreceptor exists. The design of the receptor molecule, however, has major impact on the stability and function in T cells and thereby on the efficacy of adoptive immunotherapy.

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