9 Summary

Grafting T cells with new antigen specificity by T cell receptor (TCR) gene transfer could greatly facilitate adoptive T cell immunotherapy. TCR-redirected T cells possess exogenous and endogenous TCR. Little is known about how two TCR on one T cell influence each other. This is often due to the fact that the specificity of the endogenous TCR is unknown. Major questions are, whether exogenous and endogenous TCR chains develop hybrid TCR and consequently new specificities and whether dual-TCR T cells, which were activated through one TCR can use the second TCR for effector functions. Mice, which are transgenic for the genes of two different TCR can generate dual-TCR T cells and allow the analysis of T cells with two known specificities. We have generated OT-I/P14 dual-TCR transgenic (Dtg) T cells specific for ovalbumin (ova257) and lymphocyte choriomeningitis virus glycoprotein (gp33) peptides. These cells can be stimulated by either antigenic peptide to proliferate and produce IFN. Even though one TCR (P14) is expressed at reduced levels on dual-TCR T cells, the peptide sensitivity of these cells is similar to that of single-TCR transgenic (Stg) T cells of the same specificity. TCR expressed by OT-I/P14 Dtg T cells consist mainly of cognate TCR-chains, although OT-I and P14 TCR chains can develop hybrid heterodimers with unknown specificities in P14/OT-I-transgenic and P14-tansduced OT-I T cells. Stimulation of one TCR on Dual-TCR-T cells does not directly influence the expression level of the second TCR. TCR down-modulation on dual-TCR T cells depends primarily on binding of the specific ligand. *In vivo,* Dtg T cells mediate effector functions via both TCR after stimulation through either TCR. Adoptively transferred Dtg T cells suppress the growth of both, B16-ova und B16-gp33 tumours, regardless of the peptide (ova257 or gp33) used for previous *in vitro* activation. The adoptive transfer of OT-I/P14 Dtg T cells induces autoimmunity in mice, which express ova as self-antigen in pancreatic -cells. Dependent on the expression level of ova, OT-I/P14 Dtg T cells induced severe (in RIP-mOva) or mild diabetes (in RIP-Ova^{lo} mice), regardless whether they were activated via the OT-I or P14 TCR. Taken together, we established a model of gene therapy to analyse conditions and consequences of functional expression of exogenous TCR genes.