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P72. Transgenic expression of a chimeric signaling receptor to facilitate T cell costimulation in the tumour environment

R Schlenker[1*], M Leisegang[2], W Uckert[2], E Noessner[1]

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Tumour therapy with T cell receptor (TCR) engineered T cells is reported to induce clinical responses but shortcomings regarding poor *in vivo* persistence and loss of function in the tumour milieu have been observed. Providing costimulation to adoptively transferred T cells may improve these shortcomings. However, human T effector cells are largely CD28 negative and epithelial tumours do not express CD80 or CD86. Therefore, costimulation of human CD8 T effector cells cannot be triggered via the classical way of CD28 ligation. We propose to facilitate costimulation of CD8 T effector cells in the tumour milieu through retroviral engineering of T cells with a chimeric signaling molecule (CSM). This CSM is consisted of an intracellular costimulatory domain fused to an extracellular domain with binding capacity for a ligand expressed by a great variety of tumours.

Human activated PBL retrovirally transduced to express the CSM exhibited a survival advantage during *in vitro* expansion according to clinical protocol. The effect of the chimeric molecule on T cell function was analyzed using T cells expressing a tumour antigen specific TCR alone or in combination with the CSM. Transduced T cells were stimulated with target cells positive or negative for the CSM ligand (CSM-L). CSM expressing T cells responded better to CSM-L$^+$ target cells showing higher phosphorylation of ERK and RPS6 compared to stimulation with CSM-L$^-$ target cells. CSM$^-$ T cells responded equally to both target cells. Accordingly, CSM$^+$ but not CSM$^-$ T cells secreted more IL-2 and IFN-γ upon co-culture with CSM-L$^+$ target cells. In summary, transduction of PBL with the chimeric signaling molecule supported T cell survival and TCR induced signaling leading to enhanced T cell function.

Authors' details
[1]Helmholtz Zentrum Muenchen, Institute of Molecular Immunology, Munich, Germany. [2]Max Delbrueck Center for Molecular Medicine, Molecular Cell Biology and Gene Therapy, Berlin, Germany.

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[1]Helmholtz Zentrum Muenchen, Institute of Molecular Immunology, Munich, Germany
Full list of author information is available at the end of the article