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Introducing a novel switchable CAR platform with reduced CAR size for immunotherapy of tumors

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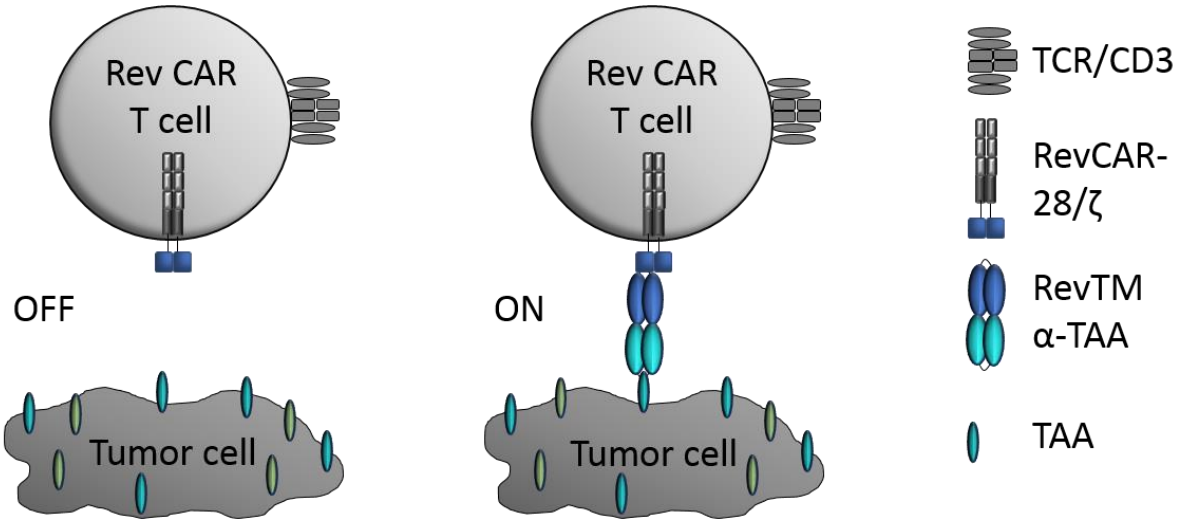

1. Introduction

Recently the use of chimeric antigen receptor (CAR) modified T cells in the immunotherapy of tumors has become a promising approach. CAR T cells are able to recognize tumor-associated antigens (TAAs) in a major histocompatibility-complex (MHC)-independent manner. Although highly efficient, the inability to regulate the activity of CAR T cells can cause severe side effects and thus needs to be considered in future developments. Here, we introduce the RevCAR system – a novel switchable modular universal CAR system having a minimal size to overcome the obstacles of conventional CAR therapy.

2. Objectives

In order to improve the controllability of CAR T cells a modular CAR system, which allows switching the activity of CAR T cells repeatedly "ON" and "OFF", was generated. Furthermore, to avoid unspecific side effects and minimize tonic signaling of conventional CAR T cells, the extracellular single chain variable fragment (scFv) was removed. Thus, resulting RevCARs have a smaller size allowing "gated" targeting strategies, e.g. by facilitating simultaneous transduction of two independent CARs with different specificities and split motifs, which could further improve the safety of CAR T cells.

3. Materials & methods

In order to reduce the size of the artificial receptor the original idea was to replace the extracellular scFv domain of a conventional CAR with a small peptide epitope and to engage the resulting RevCAR T cell via a bispecific target module which we termed RevTM. For proof of concept two small peptide epitopes were selected and the respective RevCARs constructed. In addition, a series of different RevTMs was generated. On the one hand the RevTM recognizes one of the two peptide epitopes on the other hand the RevTM can be directed to any potential TAA.

4. Results

Until now a series of RevTMs was constructed and functionally analyzed. RevCAR T cells armed via the respective RevTM were able to efficiently lyse their respective target cells in a peptide epitope and target specific, as well as target module dependent manner. These data are supported by the analysis of cytokine secretion from RevCAR T cells which was only observed in the presence of both target cells and the respective RevTM.

5. Conclusion

Taken together these results demonstrate the high anti-tumor efficiency of the novel RevCAR platform which is characterized by a small size, an improved safety, easy controllability as well as high flexibility.