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Universitat Autònoma de Barcelona

RECEPTOR (CAR)-T CELLS

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Introduction

Cancer immunotherapy based on T cells has become more relevant after discovering the participation of CD8+ and CD4+ T cells in the recognition and destruction of malignant cells. **Genetic modification** of T cells by viral or non-viral methods allows the generation of specific T cells for tumor-associated antigens (TAA) populations. One option to genetically modify T cells consists in using **classical T cell receptors** (TCRs) with known specificity and affinity. The main drawback is that the chimeric TCR formation may lead to a change in specificity, triggering an autoimmune reaction. Furthermore, each transgenic TCR is specific for a given peptide-MHC complex meaning that some mechanisms of tumor-mediated immune evasion may limit the success of this approach.

Defining a CAR

Chimeric antigen receptors (CARs) combine an **antigen-binding region** from a molecule able to bind strongly to antigens (usually consisting of a single-chain variable fragment derived from a monoclonal antibody) and **cytoplasmic domains** from conventional immune receptors. CARs **can overcome limitations** associated with the use of classical TCRs as they allow greater tumor regression while not diminishing T cells efficiency, both in terms of recognition and removal of tumor cells.

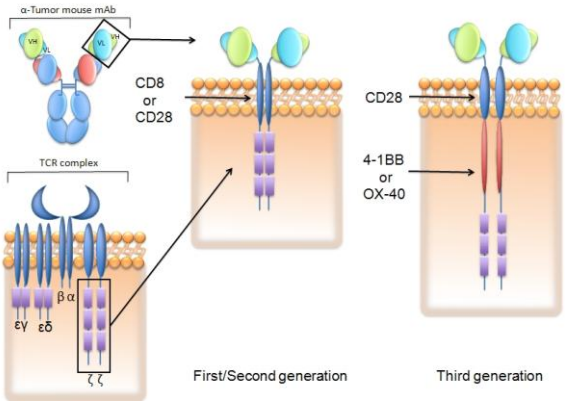

Figure 1. The basic structure of a monoclonal antibody (mAb)-derived chimeric antigen receptor (CAR). Chekmasova *et al*., 2010.

Pros and Cons of a CAR

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Antigen recognition and processing are **independent of the HLA system** → use in patients with **different haplotypes** + **avoidance** of tumor mechanisms of **immune evasion**.

Able to recognize **non-peptidic antigens** such as carbohydrates or glycolipids.

Its use **does not involve the risk of triggering unexpected and potentially harmful specificities** (individual molecules which do not interact with native TCR chains).

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Only able to recognize **surface antigens** vs. Intra- and extracellular antigens (TCR).

Clinical Trials

SOLID TUMORS

First completed phase I clinical trial: CAR T-cells directed against the folate receptor-α (ovarian tumor antigen). **Results**: a high number of T cells with specific CARs could be administrated safely to patients with epithelial ovarian cancer. Although these cells did not prevail long term.

Clinical trials have been carried out for the treatment of **other cancers** such as colorectal and gastrointestinal, renal, breast, prostate and melanoma.

LIQUID TUMORS

First published study involving a specific CAR: CAR T-cells directed against CD20 (Hodgkin lymphoma). **Results**: no toxicity or adverse effects were observed and no immune response was detected (mitigated in patients treated with chemotherapy or immunosuppression).

Several clinical trials have been carried out directing CARs against CD19 (lymphoma antigen).

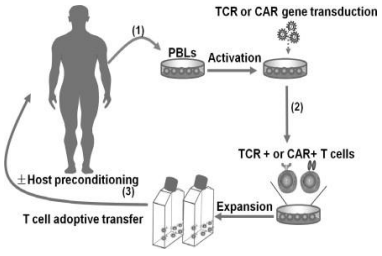

Figure 2. Transfer of genetically modified T cells. Shi *et al*., 2013.

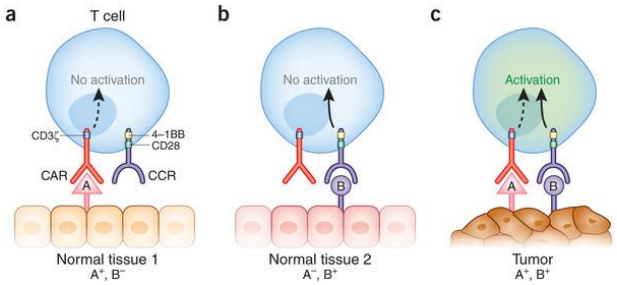

Figure 3. Mechanism of double recognition. Hanada *et al*., 2013.

Double recognition

T cells engineered to express a CAR and a **chimeric co-stimulatory receptor** (CCR) could enhance the tumor specificity of targeted T cell therapies. This **double recognition** has been tested with CARs and CCRs directed against PSMA and PSCA. Both are antigens present in prostate cancer cells.

Future Prospects

Treatment of cancer with CAR T-cells has **significant advantages**. The therapy success will depend mainly on the identification of **tumor-specific antigens**, minimizing the risk of toxicity. Achieving **optimal dose and duration** of the treatment will increase clinical trials efficiency Another challenge will consist in improving **in vivo persistence** of modified T cells after transfer. Recent studies applying this technique in hematological diseases have succeeded but **therapy in solid tumors needs to be improved** (anergy and apoptosis are induced by the tumor microenvironment).

It can be stated that CARs have potential therapeutic uses. **Further study in this area will be needed** to overcome current limitations and to increase the therapy success.

References

Shi H, Liu L, Wang Z. 2013. Improving the efficacy and safety of engineered T cell therapy for cancer. Cancer Lett 328(2): 191-7 **; Hanada K, Restifo NP**. 2013. Double or nothing on cancer immunotherapy. Nat Biotechnol 31(1): 33-4 **; Ramos CA, Dotti G**. 2011. Chimeric antigen receptor (CAR)-engineered lymphocytes for cancer therapy. Expert Opinion on Biological Therapy 11(7): 855–73 **; Chekmasova AA, Brentjens RJ**. 2010. Adoptive T cell immunotherapy strategies for the treatment of patients with ovarian cancer. Discov Me 9(44): 62-70.