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.

Pros and Cons of a CAR

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).

Only able to recognize surface antigens vs. Intracellular 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).

Future Prospects

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.

References