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Editorial

Chimeric Antigen Receptor: Targeting 5T4 Antigen Tumor in Ovarian Cancer Therapy

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DESCRIPTION

Chimeric antigen receptor (CAR) T-cells represent a novel targeted approach to overcome both quantitative and qualitative shortfalls of the host immune system relating to the detection and subsequent destruction of tumors. The identification of antigens expressed specifically on the surface of tumor cells is a critical first step in the ability to utilize CAR T-cells for the treatment of cancer. The 5T4 is a tumor-associated antigen which is expressed on the cell surface of most solid tumors including ovarian cancer. 12 patients with ovarian cancer had their blood and tumour samples matched, and all tumours tested positive for 5T4 expression by immunohistochemistry.

Two distinct anti-5T4 CAR designs were successfully transduced into patient T-cells, each with a different affinity for the target antigen. Antigen-specific IFN-gamma production was observed when CAR T-cells were co-cultured with matched autologous tumour disaggregates.

In addition, a mouse model used to test the efficiency of anti-5T4 CAR T-cells showed therapeutic advantage against existing ovarian cancers.

T-cells that have been genetically modified to express chimeric antigen receptors (CARs) can form effector populations with determined antigen specificities that are not restricted by the native T-cell receptor.

The capacity to redirect a patient's T-cells specificity to recognise an antigen expressed on their tumour allows for the delivery of a therapeutically relevant dose of antigen-specific T-cells. In its simplest form (so called first-generation CARs), an immunoglobulin-derived single-chain variable fragment (scFv) specific for the antigen of choice is fused to the CD3 signaling domain of the T-cell receptor complex to facilitate T-cell activation. Later generation CARs include ≥1 costimulatory domains such as CD28 or 4-1BB, which promote expansion and survival of the CAR T-cells in vivo. Recent trials of CAR T-cells in patients with hematological malignancies have demonstrated impressive clinical responses. For example, several groups have reported response rates of >80% using CAR T-cells targeting the CD19 antigen, which is expressed on several B-cell malignancies including B-acute lymphoblastic leukemia. Trials are ongoing to determine these responses can be replicated in solid tumors; however, to date the data emerging from studies in solid tumors have been less compelling. The reason for the difference in clinical responses is likely to be related to the unique challenges posed by solid tumors, such as the requirement for the CAR T-cells to home to the tumor site and the presence of immunosuppressive cells within the tumor microenvironment. Despite these issues, a growing number of clinical trials are being initiated which target antigens expressed on the surface of solid tumors, for example HER2, CEA, EGFR, Mesothelin, and GD2. Currently, there is no consensus on the best CAR construct to use for the treatment of solid tumors. Although there is evidence that the addition of costimulatory domains (eg, CD28 or 4-1BB) to first-generation CARs enhanced cytotoxicity and T-cell persistence, more head-to-head comparisons are needed before clear conclusions can be drawn.

In addition to the expression profile of the target antigen, the affinity of the antibody used to generate the CAR is another factor that could affect safety. Several publications have reported that the affinity of the scFv could affect functional responses of the CAR T-cells. For example, it has been shown that a high-affinity CAR-targeting folate receptor β exhibited enhanced antitumor activity both *in vitro* and *in vivo* compared with a lower affinity CAR. However, other researchers have demonstrated that by decreasing the affinity of antibodies with known off-tumor toxicity issues (eg, ErbB2, EGFR), they were able to maintain the therapeutic index while decreasing reactivity against normal tissues expressing the target antigen.

One tumor-associated antigen which could be an attractive target for a CAR T-cell in solid tumors is 5T4. The 5T4 oncofetal antigen was first identified by searching for surface molecules shared between human trophoblasts and cancer cells with the rationale that they may function to allow survival of the fetus as a semiallograft in the mother, or a tumor in its host. The 5T4 is a 72-kDa transmembrane protein expressed on the placenta and a wide range of human carcinomas including ovarian, prostate, renal.

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Gene for 5T4 encodes a 42-kDa trans membrane protein core which contains several leucine-rich repeats that are associated with protein-protein interactions. The extracellular part of the molecule contains leucine-rich repeats in 2 domains separated by a short hydrophilic sequence; there is a transmembrane domain and a short cytoplasmic sequence. When human 5T4 was overexpressed in murine fibroblasts the cells became more spindle shaped and had reduced adherence, whereas in normal epithelial cells there was E-cadherin down regulation, increased motility, and cytoskeletal disruption. The cytoskeletal disruption through 5T4 overexpression is dependent on the 5T4 cytoplasmic domain, which interacts with TIP2/GIPC, known to mediate links to the actin cytoskeleton. These studies were the first to indicate a possible association of 5T4 expression with cancer spread.

Ovarian cancer remains the most lethal gynecologic malignancy with a 5-year survival of 40% for patients with advanced disease. Most patients with advanced disease will have an initial favorable response to cytoreductive surgery and platinum-based chemotherapy; however, ultimately 80% of patients relapse within 18 months of completion of first-line treatment. Advances in traditional cytotoxic chemotherapy such as intraperitoneal administration, dose-dense schedules, and the addition of targeted therapies including bevacizumab have improved progression-free survival but have failed to have a significant effect on overall survival rates. There is extensive evidence that ovarian cancer is under immune surveillance. Multiple studies have demonstrated a positive correlation between the number of CD3+ tumor-infiltrating lymphocytes and overall survival. Similarly, high frequencies of immune effector cells such as CD8+ T-cells and natural killer cells have also been shown to correlate with positive clinical outcomes. Such observations suggest that immune-targeted approaches in ovarian cancer could deliver therapeutic benefit. The folate receptor was employed as a target in the first CAR T-cell experiments targeting ovarian cancer.