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COMMENTARY

Adoptive Cell Transfer to Enhance Patients Immunity Against Cancer

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ABSTRACT

Cancer is an abnormality of cells in which cells are proliferating in an uncontrolled manner due to some unwanted mutations. Any cells from any part of body can be cancerous and may form tumors later on. These tumors develop tumorsphere and their microenvironment modulate T cells as a survival mechanism and these immune cells failed to identify the cancerous cells, allowing them to metastasis. A number of therapeutic approaches such as radiotherapy, chemotherapy etc. are being applied in clinical practices to remove tumors or kill tumor cells. Cell therapy has shown a promising potential in last two decades in cancer treatment as some cells such as mesenchymal stem cells have tumor tropism and induce apoptosis in cancer cells. Recently, immunotherapeutic approaches have been considered the gold standard and it has been shown that T cells isolated from the cancer patient can be trained to target cancer cells. In this process, chimeric antibody receptor (CAR) and T-cell receptor (TCR) are introduced on the T cell surface to enhance T cells function and their transfer in the patient's circulatory system result in the identification and killing of cancerous cells. This approach has been known as the adoptive cell transfer or adoptive cell therapy (T cells) and has shown 99% promising results in 243 clinical trials done so far. Clinical trials are going on to determine its efficacy in cancer treatment and a number of pharmaceutical firms are developing adoptive T cells as drugs to treat cancer in our daily routine clinical practice. Results obtained yet, have shown the perspective of adoptive cell therapy as the future approved cancer therapy.

Keywords: Adoptive Cell Therapy, Adoptive T-Cell Transfusion, Cell Therapy, Clinical Trials, Cancer Therapy

Cancer is the second largest cause of mortality around the world causing millions of deaths every year (1). It is caused when cells failed to follow the cell cycle checkpoint pathways and start dividing in an uncontrolled manner. Millions of cells are dying daily, and these cells are being replaced by newly divided cells to regulate body functions normally. By some unwanted mutations, the cells skip the controlled and regulated division mechanism and start developing massive structures containing cancer cells called tumors (2, 3). As these mutations are making cells abnormal or cancerous, T cells of body are aimed to kill the cancerous cells whenever they developed in any part of the body.

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When the number of abnormal or cancer cells increasing rapidly, these cells as a part of their survival mechanism, start to modulate T cell function and these modulated T cells failed to skip the cancerous cells allowing them to grow rapidly leading to metastasis (4).

Cancer Therapies

Cancer is being treated in clinics by a number of routine therapeutic approaches such as chemotherapy, radiation therapy etc. These approaches are not just targeting the cancer cells but also harming the normal cells. To target cancer cells only in the patient's body, struggle towards targeted cancer therapy focusing specific cancer cells has been made and modern therapeutic approaches such as cell therapy and gene therapy are gaining attention of researchers and clinicians around the world (5). Adoptive cell therapy which is also known as adoptive T cell therapy is the transfusion of lymphocytes used to treat cancer and chronic infections. In this approach, immunity of the body is enhanced to fight against diseases such as cancer and T cells are trained for this purpose (6).

Adoptive Cell Transfer (Adoptive Cell Therapy)

It has been proposed that an improved way of immunotherapy based on T-cell training (adoptive cell therapy) is a promising approach for targeted cancer therapy which is in current phase facing a number of challenges such as isolation of autologous lymphocytes and their *ex vivo* expansion, their manipulation to express tumor specific T cell receptors and introduction of chimeric antigen receptor and their mode of delivery for targeted action etc. T-cell homing and cellular infiltration in the tumor sites are also the continuous challenge being faced by the researchers and a number of strategies have been proposed for clinical settings to enhance immunotherapy based on T cells (7).

In this kind of immunotherapies, T cells are trained for enhanced action against malignant cells. Most appropriate T cells for this purposes are tumor-specific T cells which are modulated under the influence of tumor cells and diverted themselves from their job to identify and kill tumor cells (8)**.** So, training T cells following adoptive cell therapy is an attractive approach not just for cancer problems but also for some autoimmune and inflammatory problems such as Crohn's disease (CD) (9). Their very promising clinical results have attracted pharmaceutical industry to invest in the area of adoptive cell therapy and regulator challenges for its commercialization has been discussed clearly (10). Adoptive cell therapy includes adoptive transfusion of tumor-infiltrating lymphocytes (TILs) and development of genetically engineered T lymphocytes expressing chimeric antigen receptors (CARs) or conventional alpha/beta T-cell receptors (TCRs). Maintaining current good manufacturing practices (cGMPs) is a critical step in the commercialization of adoptive cell therapy which is a novel approach with promising results in cancer. Clinical grade production of TILs at large-scale as well as the regulatory pathways to ease the adoptive T cells are the current topic of discussion (11).

Production of Adoptive T Cells

Adoptive T cells are autologous activated antitumor T cells which are manufactured and expanded *ex vivo* for targeted cancer therapy. Currently there are three approaches to generate adoptive cells for targeted cell therapy against tumor; 1) production of tumor-reactive tumor-infiltrating lymphocytes (TILs), isolated, activated and expanded ex vivo (12), (2) Genetic engineering approach to introduce T-cell receptors (TCRs) or tumor-recognizing chimeric antigen receptors (CARs) on the surface of autologous peripheral blood T cells (13-15) and (3) production of viral specific T cells to treat virus-related malignancies. There are two such types of T cells have been generated successfully by a number of research laboratories around the world known as tri-viral-specific and penta-viral-specific T lymphocytes in which T cells are infused with Epstein–Barr virus (EBV), cytomegalovirus,

adenovirus and CMV, AdV, EBV, BK virus (BK) and human herpes virus 6 (HHP6) respectively. G-Rex bioreactors are used for continuous culture of these cells in the presence of IL-4 and IL-7 (11). Engineering principle to adopt T cells for TCR and CAR is shown in figure 1.

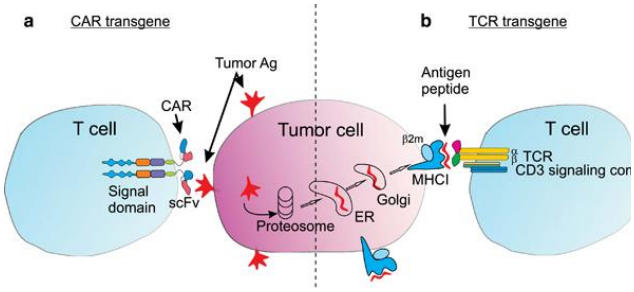

Figure 1: Engineering principle for TCR and CAR based T cell engineering (doi:10.1038/cgt.2014.81)

Future Perspectives

Adoptive cell transfer which is also known as adoptive cell therapy which is the reactivation and transfer of modulated T cells of cancer patients (16). In this process, Tumor-infiltrating lymphocytes (TILs) or genetically engineered T cells are trained to express CARs or TCRs on their cell surfaces. These trained cells are then introduced in the patient's circulatory system to find out the cancerous cells in the body and kill them. The manufacture of cellular products under current good manufacturing practices (cGMPs) for commercial applications is under process by a number of pharamacutical firms working for the large-scale production of clinical-grade cells (i.e. TILs, virus-specific and genetically modified CAR or TCR transduced T cells) to bring these cellular products in clinics (17). Adoptive T cells have also been applied in combination with vaccines and have shown very promising results in pre-clinical studies (18). Further clinical trials are going on to determine its efficacy in cancer treatment and results obtained yet, have shown the perspective of adoptive cell therapy as the future approved cancer therapy (19).

Conflict of Interest

Authors declare no conflict of interest with any person or organization regarding this manuscript. Figure used in this paper, is obtained from an open access article and the reference is given on the figure caption.

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